NOT FOR PUBLICATION

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PURDUE PHARMACEUTICAL PRODUCTS L.P. et al., Plaintiffs, v. ACTAVIS ELIZABETH LLC, et al., Defendants.	Civil Action No. 12-5311 (JLL) (JAD) **OPINION**

LINARES, District Judge.

This case involves the issues of infringement and validity of three patents covering Plaintiffs' product Intermezzo®. Intermezzo® is a drug manufactured for the treatment of insomnia when middle-of-the-night awakening is followed by difficulty returning to sleep. After careful consideration of the evidence presented at a bench trial held December 1 -15, 2014, the Court finds as follows: As to the '131 patent, Defendants have met their burden of proving this patent is invalid as obvious, but failed to prove that the claim element "without residual sedative effects" is invalid as indefinite. Plaintiffs have proved by a preponderance of the evidence that the asserted claims of the '131 patent are infringed by all Defendants. As to the '628 patent, Plaintiffs have failed to meet their burden of proving infringement as to Defendants, DRL and Actavis. Plaintiffs, however, have met their burden of proving that Novel infringes the '628 patent. While Defendants have failed to prove this patent is invalid as anticipated, the '628 patent is invalid as obvious. As to the '809 patent, Plaintiffs have met their burden of proving infringement as to

Defendants, DRL and Novel. Defendants, on the other hand, have proved by clear and convincing evidence that the '809 patent is obvious and therefore invalid. This Opinion articulates the basis for each of these conclusions.

INTRODUCTION

This is an infringement action brought by Plaintiffs relating to the patents covering Intermezzo®. This action was commenced as a result of Defendants each filing an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act, seeking FDA approval to sell a generic version of Intermezzo® prior to the expiration of the relevant patents. This Court has subject matter jurisdiction over this action under 28 U.S.C. §§ 1331 and 1338(a). No party contests personal jurisdiction or venue for the purposes of this civil action.

BACKGROUND[1]

I. The Parties

Plaintiffs, Purdue Pharma L.P., and Purdue Pharmaceutical Products L.P., are the current holders of New Drug Application No. 022328, for sublingual tablets containing 1.75 mg and 3.5 mg of zolpidem tartrate. These Plaintiffs market the approved drug under the tradename Intermezzo®. Plaintiff, Transcept Pharmaceuticals, Inc., ("Transcept"), is the owner of the relevant patents where Purdue Pharma L.P., and Purdue Pharmaceutical Products L.P.[2] are exclusive licensees under these patents. Plaintiffs offer that Transcept is currently known as "Paratek Pharmaceuticals, Inc." (*See e.g.* Pls.' Proposed Findings of Fact, ("PFOF") ¶42). The

[1] The facts set forth herein are the Court's findings of facts which are based on the Court's observations and credibility determinations of the witnesses who testified and a thorough review of all the evidence admitted at trial.

[2] Transcept Pharmaceuticals, Inc., Purdue Pharma L.P., and Purdue Pharmaceutical Products L.P, will collectively be referred to as "Plaintiffs."

Court, however, for purposes of this Opinion, refers to the named assignee of the patents-in-suit as "Transcept."

While there are five Defendants in this action, two of said Defendants, Par Pharmaceutical, Inc. (hereinafter "Par"), and TWi Pharmaceuticals, Inc. (hereinafter "TWi"), entered into stipulations wherein both agreed to be bound by the outcome of the trial without them actually participating. That is, TWi "agree[s] to be bound by the Final Judgment … including any related injunctions, of the District Court in the Intermezzo Action resolving all claims and counterclaims of infringement, validity and enforceability of the '131 patent following litigation on the merits." (Stipulation, ECF No. 332, ¶4). Similarly, Par, "agree[s] to be bound by the Final Judgment … including any related injunctions, of the District Court in the Intermezzo Action resolving all claims and counterclaims of infringement, validity and enforceability of the '131 and '809 patents following litigation on the merits." (Stipulation, ECF No. 323, ¶3). Both TWi and Par stipulated to personal jurisdiction for purposes of this action. The remaining Defendants in this action are Actavis Elizabeth, LLC (hereinafter "Actavis"), Dr. Reddy's Laboratories, Inc., and Dr. Reddy's Laboratories, LTD, (hereinafter collectively "Dr. Reddy's" or "DRL"), and Novel Laboratories, Inc., (hereinafter "Novel").

II. Intermezzo and the Patents-in-Suit

Intermezzo® is a drug manufactured for the treatment of insomnia when middle-of-the-night (or "MOTN") awakening is followed by difficulty returning to sleep. (PTX-225 at 1). Intermezzo® is intended for use only if the patient has four hours or more remaining before the planned time of waking. Intermezzo® is in the form of a tablet that is placed under the tongue to disintegrate. This formulation is for transmucosal absorption. The three relevant patents at issue

covering Intermezzo are U.S. Patent No. 8,242,131 (the "'131 patent"), U.S. Patent No. 7,682,628 (the "'628 patent"), and U.S. Patent No. 8,525,809 (the "'809 patent"). Nikhilesh N. Singh is the sole named inventor of each of the three relevant patents, except regarding the '131 patent only, where Sathasivan Indiran Pather is named as a co-inventor.

The '809 patent is a patent indicated for the treatment of MOTN insomnia. The '131 patent is directed to a method of treating MOTN insomnia where the '628 patent is directed to a method of treating insomnia. The '131 Patent is entitled "Methods of Treating Middle-of-the-Night Insomnia" and was issued by the PTO on August 14, 2012. The '628 Patent is entitled "Compositions for Delivering Hypnotic Agents Across the Oral Mucosa and Methods of Use Thereof" and was issued by the United States Patent and Trademark Office ("PTO") on March 23, 2010. The '809 Patent is entitled "Compositions for Treating Insomnia" and was issued by the PTO on August 28, 2012. The priority dates are: 1) for the '628 Patent, February 17, 2004; 2) for the '131 Patent, May 25, 2005; and 3) for the '809 Patent, May 25, 2005.

III. The Claims at Issue and Relevant Markman Construction

A. Claims of the '131 Patent

Plaintiffs claim all Defendants will induce infringement of Claims 8, 10, 18 and 19 of the '131 patent. Because Claims 1 and 12 of the '131 patent are independent claims, and therefore Claims 8, 10, 18, and 19 depend therefrom, a detailed analysis of Claims 1 and 12 is applicable to the infringement and validity inquiries. Claims 1 and 12 are distinct insofar as Claim 1 applies to non-elderly patients and Claim 12 applies to elderly patients. Defendants argue that that the claims of the '131 patent are obvious. Defendants also argue that limitation found in Claims 1 and 12, namely, "without residual sedative effects" is indefinite. These claims state the following:

> Claim 1: A method of treating middle-of-the night insomnia in a non-elderly patient without prophylactically administering zolpidem, comprising: dosing the patient with a pharmaceutical composition comprising about 0.5 to about 4.75 mg of zolpidem hemitartrate or a molar equivalent amount of a pharmaceutically acceptable form of zolpidem, wherein the pharmaceutical composition is substantially free of other hypnotic agents, wherein the patient awakens from sleep and desires to resume sleep for less than 5 hours, wherein the step of dosing the pharmaceutical composition is performed after the patient awakens from sleep, and wherein the pharmaceutical composition permits the patient to awaken at a time about four hours after dosing without residual sedative effects.
>
> Claim 12: A method of treating middle-of-the-night insomnia in an elderly patient without prophylactically administering zolpidem, comprising dosing the patient with a pharmaceutical composition comprising about 1.5 to 2.5 mg of zolpidem hemitartrate or a molar equivalent amount of a pharmaceutically acceptable form of zolpidem, wherein the pharmaceutical composition is substantially free of other hypnotic agents, wherein the patient awakens from sleep, and desires to resume sleep for less than 5 hours, wherein the step of dosing the pharmaceutical composition is performed after the patient awakens from sleep, and wherein the pharmaceutical composition permits the patient to awaken at a time about four hours after dosing without residual sedative effects.

This Court construed "without residual sedative effects" to mean "with no or minimal subjective feelings of sedation, as evaluated by: (a) testing acceptably in at least one test exploring psychomotor performance, attention, information processing, and memory used by those of skill in the art; and/or (b) demonstrating plasma levels of zolpidem, at an appropriate time point, below about 20 ng/ml." (Opinion, ECF No. 185 at 5-7). A list of appropriate psychomotor performance, attention, information processing, and memory used by those of skill in the art are exemplified in the patent specification.

Claim 8 depends from Claim 1 and is substantially identical to such except it refers to the 3.5mg dose. (JTX 1, Claim 8). Claim 10 of the '131 Patent recites: "The method of claim 8, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa." (JTX 1, Claim 10). Claim 18 depends from Claim 12 and is substantially identical to such except it refers to the 1.75mg dose. Claim 19 of the '131 Patent recites: "The method of Claim 18, wherein the pharmaceutical composition provides delivery of zolpidem across the patient's oral mucosa."

B. Claims of the '628 Patent

Plaintiffs claim Defendants will induce infringement of Claims 9, 16 and 17 of the '628 patent. The '628 patent contains an independent Claim 1 which states the following:

> Claim 1: A method for treating insomnia, comprising the steps of: administering a solid pharmaceutical composition comprising zolpidem or a pharmaceutically acceptable salt thereof to a subject prone to insomnia, the pharmaceutical composition further comprising a buffer, wherein the buffer raises the pH of saliva to a pH of about 7.8 or greater, wherein zolpidem is absorbed across a permeable membrane of the subject's oral mucosa, and wherein at least 75% of the solid pharmaceutical composition dissolves within 10 minutes or less within an oral cavity following administration.

Claim 9 of the '628 Patent recites as follows: "The method of claim 1, wherein the buffer comprises a carbonate buffer and a bicarbonate buffer." (JTX 003, Claim 9). Claim 16 of the '628 Patent recites as follows: "The method of claim 1, wherein the zolpidem or pharmaceutically acceptable salt thereof is in an amount from about 1 mg to about 5 mg." (JTX 003, Claim 16). Claim 17 of the '628 Patent recites: "The method of claim 1, wherein the zolpidem or pharmaceutically acceptable salt thereof is in an amount from about 2 mg to about 5 mg." (JTX 003, Claim 17).

C. Claims of the ’809 Patent

Claim 1 of the ’809 Patent, upon which asserted Claims 11, 17, and 18 depend, recites as follows:

> A solid unit dosage composition for the treatment of MOTN insomnia, said composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across a subject’s oral mucosa, wherein said effective amount is an amount of less than 1.30 x 10-5 moles of zolpidem, and between about 25 ng/mL and about 50 ng/mL within 20 minutes of administration, when evaluated in an appropriate patient population.

Claim 11 of the ’809 Patent recites: “The solid unit dosage composition of claim 1, wherein the zolpidem is delivered across at least one of the sublingual or buccal mucosa.” Claim 17 of the ’809 Patent recites: “The solid unit dosage composition as in any of claims 1–6, 15, or 16, containing about 1.75 mg of zolpidem hemitartrate.” Claim 18 of the ’809 Patent recites: “the solid unit dosage composition as in any of claims 1–6, 15, or 16, containing about 3.5 mg of zolpidem hemitartrate.” Claim 12 of the ’809 Patent, upon which asserted Claim 22 depends, recites:

> A solid unit dosage composition for the treatment of MOTN insomnia, said composition comprising an effective amount of zolpidem or a salt thereof and at least one buffering agent, formulated for delivery of zolpidem across a subject’s oral mucosa, wherein said effective amount is 0.5 to 4.75mg of zolpidem hemitartrate, and is an amount sufficient to produce a plasma concentration between about 25 ng/mL and about 50 ng/mL within 20 minutes of administration, when evaluated in an appropriate patient population.

Claim 22 of the ’809 Patent recites: “The solid unit dosage composition of claim 12, further comprising a binary buffer system that raises the pH of said subject’s saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva.”

“Binary buffer system” was construed by the Court to mean “a system used to maintain and/or achieve an approximate pH range comprising at least one proton-donating component and at least one proton accepting component.” (Opinion, ECF No. 185 at 26). This element is similar

to the "buffer" element of the '628 patent except it is somewhat more specific as it refers to a "system."

IV. Procedural History

The original Complaint in this action was filed on August 23, 2012 against Defendant, Actavis. By February 26, 2014, all actions brought by Plaintiffs relevant to Intermezzo® and patent infringement were consolidated. Each of the Defendants represented to the Court that it will not launch its ANDA product prior to March 31, 2015. The consolidated action against Actavis, DRL, and Novel was heard by the Court at a bench trial on December 1–15, 2014.

V. MOTN Insomnia

Insomnia is a common malady that occurs in approximately one third of the adult population. (*See* JTX 016). The term insomnia is used to describe all conditions related to the patient's perception of inadequate or non-restful sleep. (Tr. 7.136:17-21 (Winkelman)).[3] Insomnia possesses three elements of difficulty: falling asleep, staying asleep, or waking up too early in the morning. (Tr. 7.133:16-21 (Winkelman)). Prior to 2005, the method of treating all types of insomnia was primarily through prophylactic administration to prevent insomnia rather than on the "as needed" basis described in the '131 patent. Middle-of-the-night insomnia was construed by the Court to be a "condition wherein a subject, after falling asleep, awakens and has difficulty returning to sleep." (ECF No. 92 at 2). In sum, those who suffer from MOTN insomnia suffer from frequent nocturnal awakenings.

[3] "Tr.," refers to the bench trial transcript.

While prophylactic administration made sense for those who had trouble initially falling asleep, patients suffering from MOTN insomnia irregularly were in some cases medicating themselves unnecessarily because whether they would wake in the middle-of-the-night on that particular night was unpredictable. The treatment for MOTN insomnia (as opposed to other forms of insomnia) also presented an obstacle as the ability to get a person back to sleep in the middle of the night rather than before bed, was assumed at one point to be at least slightly more difficult because a person's drive to sleep is lessened.

Indeed, overall propensity or drive to sleep depends on the interaction between two biological processes: the homeostatic sleep drive and circadian drive. (Tr. 10.32:10–10.33:7 Czeisler)). Homeostatic sleep drive increases with every waking hour, but when a person falls asleep, homeostatic sleep drive declines, such that by the middle of the night, much of homeostatic sleep drive is dissipated. (Tr. 10:35:4–24 (Czeisler)). On the other hand, the circadian drive is governed by a biological clock that sends out a signal to wake or be alert during the day and a signal to quiet the drive to wake at night. (Tr. 10.37:16–10.39:19 (Czeisler)). The circadian drive promotes waking during the day (as the circadian signal for alertness increases) and promotes sleep (or the absence of waking) through the night (as the circadian signal for alertness decreases). (Tr. 10.37:16–10.39:19, 10.44:19–10.45:14 (Czeisler)).

But these processes must be reconciled with the average person who sleep for eight straight hours. In other words, what keeps them asleep when their homeostatic sleep drive is decreasing by the hour? Ultimately the conclusion inevitably drawn is that the circadian signal keeps someone asleep.[4] In any event, to skilled artisans, the interaction of these processes results in a person's

[4] Indeed, this was the only plausible explanation provided to the Court for how a person sleeps *stays* asleep. (Tr. 7.133:10-11).

overall urge—or drive to sleep—to be the greatest at bedtime (as opposed to the middle of the night).

VI. Ambien®/Zolpidem

Physicians and psychiatrists were routinely prescribing the drug Ambien® to treat insomnia, prior to the filing of the patents-in-suit. (Tr. 2.93:13-20 (Ocalssen)). The active ingredient in Ambien® is the same as that in Intermezzo®, zolpidem tartrate. As of 2004, Ambien® was commercially available and prescribed in two dosages, a 10 mg tablet for non-elderly patients and a 5 mg tablet for the elderly. (JTX 41 at DRL0013528). Ambien®'s dosing information indicates that the elderly are dosed with half the normal dose as they may be especially sensitive to the effects of zolpidem tartrate. This is consistent with the general understanding that elderly people are more sensitive to the side effects of medications and metabolize drugs differently (usually more slowly) causing medications to reside in the body at high levels for longer. (Tr. 7.126:2-12 Winkelman)).

Ambien® was an incredibly successful drug commercially, which stimulated the medical research community to extensively investigate and review zolpidem. Undeniably, by 2004 the prevailing view amongst medical professionals was that zolpidem was well tolerated and posed minimal risk of abuse and dependence at the therapeutic doses of 5 mg and 10 mg. Ambien®, through its label, was indicated for prophylactic administration. While it unclear how common the practice was, at least *some* doctors were prescribing fractional (half of one) Ambien® to treat MOTN insomnia prior to 2004. (Tr. at 2.78:7-21 (Oclassen), 7.145:19-7.147:10, 7.149:23-7.150:23 (Winkelman)). This is likely because Ambien® was known by 2004 to be a safe/effective

sleep drug but more importantly, have a short duration of action of about 4 hours. (Tr. 2.75:14-16 (Oclassen), 6.161:11-21 (Michniak-Kohn), 7.143:16-7.144:10 (Winkelman)).

VII. Zolpidem v. Zaleplon

As a general proposition medication will be gone from the body in three half-lives. (Tr. 1.161:21-1.62:9 (Kryger)). While zolpidem was known to have a rapid onset and short half-life of about two to three hours, another hypnotic, zaleplon, was known to have an even shorter half-life of just one hour. Zaleplon is the active ingredient in the sleeping pill Sonata®, which around 2001, was a "comparatively new medication." (JTX 033 at 116). Pertinent articles and studies prior to 2004 were predomininantly limited to analyzing zolpidem and zaleplon, therefore suggesting that these two hypnotics were the only current effective options to treat insomnia. While on the surface it may seem as though zaleplon's ultra short half life could be ideal for treatment in the middle of the night to avoid morning residual sedative effects, zaleplon proved unsatisfactory as the risk of waking up again was identified. (Tr. 1.161:21-1.162:9 (Kryger)). Particularly when analyzed according to the indication of Intermezzo®, which targeted patients who woke up in the middle of the night with at least four hours of sleep remaining, Sonata®, zaleplon, was too short acting, where a patient could not count on getting four hours of sleep. (Tr. 7.156:22-24 (Winkelman); *see also Teitelbaum* (PTX 033: "[M]ost FMS patients I have treated with Sonata have *not* found it to be helpful. I think Ambien is better." (emphasis in original)).

VIII. Dosage Strength of Hypnotics

Given the prophylactic nature of administration of hypnotics such as zolpidem and zaleplon prior to 2004, the dosage strengths of such were usually 5mg for an elderly patient and 10mg for non-elderly. The primary goal of hypnotics, as with many drugs, was to find the lowest effective

dose to prevent overmedicating without compromising the dose's efficacy. Similarly, for safety reasons, any dose of a hypnotic should leave a patient without a "hangover" in the morning, meaning they are free from residual sedative effects. For example, in the morning many patients would wake up and then drive to work. Driving while experiencing residual sedative effects is both hazardous to the patient and the general public. This is why one method for determining if residual sedative effects are present after administration of a hypnotic, is in fact a driving test. (*See Vermeeren* study). One well-known solution for sleep experts and drug formulators to combat side effects including residual sedative effects, was to lower the amount of the hypnotic in a given dose. (*See e.g.* (Tr. 7.156:7-15 (Winkelman): *Teitelbaum* is suggesting that Ambien is the go to drug, but if a patient was too hungover "you could…reduce the dose." (Tr. 7.156:7-15 (Winkelman)). Thus, the overarching objective in treating MOTN insomnia was to strike a balance between lowering doses to avoid residual sedative effects, while maintaining a dosage strength that was effective for four hours.

IX. Transmucosal Delivery

Most medications are formulated in an oral, swallow form. However, routes of administration of a drug are changed when taking into account the indication of the treatment (for example, a drug indicated for the treatment of MOTN insomnia) and the amount of active ingredient. When taking an oral swallow pill, at least some portion of the drug will not get absorbed and in turn, goes out through the system. More specifically, when a drug endures a "first pass effect" it goes to the liver where some of it gets broken down before making its way to systemic circulation. (Tr. 7.84:2-25 (Winkelman)). Importantly, systemic circulation provides the

delivery of the drug to the brain. (Id.). Thus, the primary benefits of systemic administration in general, are that a drug will work more quickly and therefore potentially wear off more quickly.

While there are a number of methods of systemic administration, such as intravenous, skin permeation and inhalation, many are not practical for specific treatments. One more sensible and universal method involves delivery through the body's mucosal surfaces—in the mouth or nose—where there are many blood vessels close to the surface for a drug to enter directly. Within the mouth, drugs can therefore be delivered across the sublingual or buccal mucosa by "transmucosal delivery." While this method was well known prior to 2004, it was noted that not all drugs can or should be delivered this way. This is for the same reason that not all drugs—for example those that must be delivered in voluminous quantities to be efficacious—are suitable for delivery by an oral swallow tablet, either because it is an impossible route or is less beneficial.

Fortunately, for many drugs whose properties are well known (*e.g.* pharmacokinetics) and have been extensively researched and published by the medical community, formulations for transmucosal delivery became more identifiable. Pharmacokinetic behavior of a drug is in some cases an accurate parameter for determining if a drug is suitable for transmucosal delivery. By way of example, in broad terms, drugs that are considered "lipophilic" will pass more easily through membranes, a determination that can be made when the logP value is known or published. (*See e.g.* Tr. 6.156: 9-11: Zolpidem's published logP value is 2.42.). Further, a well-known theory called the Henderson-Hasselbalch principle explains that a drug can be made more lipophilic by changing the pH, using for instance, a buffer. (Tr. 5.63:7-17 (Singh)). While zolpidem contains apparent properties that are suitable for transmucosal delivery, prior to 2004 there was not a developed formulation for zolpidem in sublingual doses.

X. Trial Witnesses

The following witnesses either appeared or had their recorded deposition admitted as evidence and played at the bench trial.[5]

A. Plaintiffs' Witnesses

1. Meir Kryger, M.D.

The Court accepted Dr. Kryger as an expert in sleep medicine and the clinical research and treatment of sleep disorders, including insomnia. (Tr. 1.136:4–16). Dr. Kryger is a Professor in the Department of Internal Medicine at Yale University in New Haven, Connecticut. (Tr. 1.124:7–10; PTX 11 at 1). He is also the Director of the Clinical Sleep Fellowship Program at the Yale Program of Sleep Medicine, and a practicing physician in the VA Connecticut Health System, specializing in sleep medicine. (Tr. 1.124:7–10, 1.128:12–21; PTX 11 at 1). Dr. Kryger has experience with Ambien® in clinical trials, and opined on its properties and how it was prescribed by physicians, dating from before its U.S. approval in 1992. (Tr. 10.189:12–10.190:9). Dr. Kryger was presented by Plaintiffs and testified regarding the understanding in the art concerning insomnia and MOTN insomnia and appropriate treatments of the condition at the time of the inventions claimed in the patents-in-suit. Dr. Kryger also offered opinions on invalidity (objective indicia of non-obviousness) and infringement.

[5] The Court has omitted some witnesses from this section having found their testimony either redundant or irrelevant based upon the Court's findings. The Court did however, consider *all* of the testimony at trial to make such findings.

2. Charles Czeisler, Ph.D., M.D.

The Court accepted Dr. Czeisler as an expert in sleep and sleep disorders. (Tr. 10.24:8–15 (Czeisler)). Dr. Czeisler is the Baldino Professor of Sleep Medicine and the Director of the Division of Sleep Medicine at the Harvard Medical School, and Chief of the Division of Sleep Medicine in the Department of Medicine at the Brigham and Women's Hospital in Boston, Massachusetts. (PTX 13 at 1, 3). Dr. Czeisler opined on the physiology of the human circadian timing system and its relationship to the sleep-wake cycle.

3. David Drover, M.D., M.Sc

The Court also accepted Dr. Drover as an expert in clinical pharmacology. (Drover Tr. 2.133:21–2.134:5). Dr. Drover is a Professor of Anesthesia at Stanford University, where he has been teaching since 1995. (PTX 14 at 1, 7; Drover Tr. 2.128:1–2). He conducts research within the field of clinical pharmacology and has been involved in more than 50 clinical studies, some involving the hypnotics zaleplon and zolpidem. (Drover Tr. 2.130:18–19, 2.131:11—2.133:1). Dr. Drover testified about the pharmacokinetic properties of different dosage forms, zolpidem formulations known at the time of the inventions and those formulations claimed in the patents-in-suit.

4. James Polli, Ph.D.

The Court accepted Dr. Polli as an expert in pharmaceutics, pharmaceutical formulation, and drug delivery. (Tr. 3.39:14–20). Dr. Polli is a Professor of Pharmaceutical Sciences and the Ralph F. Shangraw Endowed Chair in Industrial Pharmacy and Pharmaceutics at the University of Maryland School of Pharmacy. (PTX 15 at 1; Tr. 3.30:18–22, 3.32:8–12). Dr. Polli gave expert testimony about drug formulation, delivery, and absorption, including of course, zolpidem.

5. Glenn Oclassen

Mr. Oclassen was a co-founder of Transcept. (Tr. 2.57:13–21.) During the development of Intermezzo, and until 2014, Mr. Oclassen was President and CEO of Transcept. (Tr. 2.57:7–12).

6. Thomas Roth, Ph.D.

Dr. Roth was a consultant to Plaintiff, Transcept during the time that it developed Intermezzo® and submitted a declaration during the prosecution of the '131 Patent. (Tr. 10.237:18–20). From 1978 to 2014, Dr. Roth was the Director of the Sleep Disorders and Research Center at Henry Ford Health Systems. (PTX 536 at 1; Tr. 10.238:22–25). Dr. Roth was deposed by Defendants in this matter on April 15, 2014.

7. James Garegnani

Mr. Garegnani's deposition testimony was admitted at trial. At the time of his deposition, Mr. Garegnani was Director of Product Development for Novel. Mr. Garegnani was Novel's Rule 30(b)(6) designee on topics related to the development of Novel's ANDA Product, the formulation of Novel's ANDA Product, and any validity analysis of prior art conducted by Novel. (Tr. 2.216:9–12).

8. Alfred Liang, Ph.D.

Mr. Liang's deposition testimony was admitted at trial. At the time of his deposition, Dr. Liang was a Director of Product Development for Actavis. (Tr. 4.77:10–11). Dr. Liang was Actavis' 30(b)(6) designee on topics related to Actavis' ANDA, the research and development

leading to Actavis' ANDA Product, and testing that Actavis did on its products and Intermezzo. (Tr. 4.77:12–15).

9. Kranthi Kumar Gorlamari

Mr. Gorlamari is a former employee of Novel, who Plaintiffs deposed in his personal capacity. (Tr. 3.6:18–21). He was a formulation scientist who worked on the development of Novel's ANDA Product. (Tr. 3.7:14–3.8:6).

10. Narayanan Badri Viswanathan, Ph.D.

Dr. Viswanathan's deposition testimony was admitted at trial. At the time of his deposition, Dr. Viswanathan was the senior director of formulations for DRL. (Tr. 4.55:1–2 (Viswanathan)). Dr. Viswanathan was DRL's Rule 30(b)(6) designee on topics related to the content of DRL's ANDA, the research and development leading to DRL's ANDA Product, the product's formulation, and DRL's knowledge of Intermezzo and the patents-in-suit. (Tr. 4.55:2–6).

B. Defendants' Witnesses

1. Bozena Michniak-Kohn, Ph.D.

Dr. Michniak-Kohn has a Ph.D. in pharmacology has practiced as a pharmacist. As a pharmacist and as a teacher, she consulted prescribing and labeling information for drugs and has formulated drugs for transmucosal delivery. Dr. Michniak-Kohn's current position is full professor with tenure in pharmaceutics at the Ernest Mario School of Pharmacy, at Rutgers, the

State University of New Jersey. (Tr. at 6.19:23-6.20:1). The Court qualified Dr. Michniak-Kohn as an expert in pharmaceutical sciences, pharmacy, pharmacology and formulation science. (Tr. at 6.30:11-16).

2. John Winkelman, Ph.D., M.D.

Dr. Winkelman is a currently a practicing physician and Chief of the Sleep Disorders Clinical Research Program at Massachusetts General Hospital. Dr. Winkelman received his Ph.D. in Psychobiology from Harvard University in Cambridge, Massachusetts in 1983 and a medical degree from Harvard Medical School in 1987. Dr. Winkelman was proffered and accepted as an expert in sleep science, sleep medicine, and the treatment of sleep disorders. (Tr. at 7.81:17-24).

3. Umesh Banakar, Ph.D.

Dr. Banakar is an independent consultant and advisor to pharmaceutical companies and governmental agencies for the development and evaluation of pharmaceutical formulations. (DTX 3021 at 1-2). He received his Ph.D. in Pharmaceutical Technology from Duquesne University in Pittsburgh, Pennsylvania and completed his post-doctorate research relating to Advances in Controlled Release Technology at the Massachusetts Institute of Technology in Boston, Massachusetts in 1989. Dr. Banakar has assisted in formulating about 10 to 15 sublingual tablets, including a zolpidem sublingual tablet commercially available outside of the United States. As a result, Dr. Banakar was proffered and accepted by the Court as an expert in the field of pharmaceutical formulations. (Tr. 4.108:15-23).

4. Jason McConville, Ph.D.

Dr. McConville is an associate professor of pharmaceutics at the College of Pharmacy at the University of New Mexico in Albuquerque, New Mexico and has over 20 years of experience in the field of drug formulation and delivery and in the field of transmucosal drug delivery. He received of Bachelor of Science with Honors in Applied Chemistry from Coventry University in Coventry, United Kingdom in 1994. (Tr. at (DTX 1000)). Dr. McConville's current area of research is transmucosal drug delivery, which incorporates all transmucosal delivery such as oral and lung transmucosal delivery. (Tr. 4.160:18-21). Dr. McConville was proffered and accepted as an expert in the field of drug formulation and delivery, and an expert in the field of transmucosal drug delivery. (Tr. 4.161:3-9).

5. Ann Kraft

Ann Kraft, appearing in her capacity as a Fed. R. Civ P. 30(b)(6) corporate designee and in her individual capacity, was deposed by Defendants in this matter on March 11, 2014 deposition. At the time of her deposition, portions of which were presented at trial via designation, Ms. Kraft was the Executive Director of Licensing and Business Development for Plaintiff, Purdue Pharma LP.

6. Margaret Moline, Ph.D.

Dr. Moline, appearing in her capacity as a Fed. R. Civ P. 30(b)(6) corporate designee and in her individual capacity, was deposed by Defendants in this matter on March 13th, 2014 deposition. At the time of her deposition, portions of which were presented at trial via designation, Dr. Moline was a Director in the Medical Research department at Purdue Pharma LP.

7. Nilesh Parikh, Ph.D.

Dr. Parikh submitted on behalf of Plaintiff, Transcept, a declaration to the U.S. Patent and Trademark Office during the prosecution of the patent application that would eventually issue as the '628 patent. (JTX 8; Tr. at 8.231:3-5 (Parikh)). Dr. Parikh was deposed by Defendants in this matter on March 31, 2014.

8. Nikilesh Singh, Ph.D.

Dr. Singh is the named inventor on each of the patents-in-suit. He is also the founder of Plaintiff Transcept. At the time of his deposition, Dr. Singh was the Senior Vice President and Chief Scientific Officer for Plaintiff Transcept. (Tr. 5.61:17-18). Dr. Singh, appearing in her capacity as a Fed. R. Civ P. 30(b)(6) corporate designee and in his individual capacity, was deposed by Defendants in this matter on March 25, 2014 deposition.

LEGAL ANALYSIS

Plaintiffs assert claims of the '131 and '628 patent against all Defendants. Plaintiffs assert the claims of the '809 patent against Novel and DRL. Defendants argue that each of the patents-in-suit is invalid as obvious. Defendants also claim the '628 patent is invalid as anticipated and the '131 patent element "without residual sedative effects" is invalid as indefinite. While it is Plaintiffs' burden to prove infringement by a preponderance of the evidence, because all patents "shall be presumed valid," 35 U.S.C. § 282, the "burden is on the party asserting invalidity [here, Defendants,] to prove it with facts supported by clear and convincing evidence." *Linear Tech Corp. v. Int'l Trade Comm'n*, 566 F.3d 1049, 1066 (Fed. Cir. 2009) (internal citations omitted).

I. Infringement

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States, or imports into the United States any patented invention during the term of the patent ...." 35 U.S.C. § 271(a). Determining infringement requires a two step inquiry. Step one requires a court to construe the disputed terms of the patent at issue and step two requires a court to compare the accused products with the properly construed claims of the patent. Step one is a question of law; step two is a question of fact. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979–81 (Fed.Cir.1995). To prove literal infringement, the patentee must show that the accused device contains every limitation in the asserted claims. *Dolly, Inc. v. Spalding & Evenflo Cos.*, 16 F.3d 394, 397 (Fed.Cir.1994). If even one limitation is missing or not met as claimed, there is no literal infringement. *Mas-Hamilton Grp. v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998)(internal citations omitted).

In Hatch-Waxman litigation, infringement cases are filed before the alleged infringing product is sold. Consequently, the infringement analysis is based on an assumed or hypothetical set of facts. Under 35 U.S.C. 271(e)(2):

> It shall be an act of infringement to submit . . . an [ANDA] for a drug claimed in a patent or the use of which is claimed in a patent, . . . if the purpose of such submission is to obtain approval . . . to engage in the commercial manufacture, use, or sale of a drug or veterinary biological product claimed in a patent or the use of which is claimed in a patent before the expiration of such patent.

Thus, the filing of an ANDA seeking approval for an indication claimed in a patent constitutes infringement under Section 271(e)(2). As summarized in Harman, *Patents and the Federal Circuit* 494 n. 161 (9th ed. 2009): "The inquiry under § 271(e)(2) is a standard infringement test. The only difference is that the allegedly infringing drug has not yet been marketed and therefore the question of infringement must focus on what the ANDA applicant will likely market if its application is

approved." *See also Warner–Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1366 (Fed.Cir.2003) ("The proper inquiry under § 271(e)(2)(A) is whether, if a particular drug were put on the market, it would infringe the relevant patent."). Further, "[t]his hypothetical inquiry is properly grounded in the ANDA application and the extensive materials typically submitted in its support." *Id.* at 1248 (quotation omitted). Therefore, it is proper for this Court to consider the ANDA itself, materials submitted by the ANDA applicant in support of its ANDA, and any other pertinent evidence. *Id.* at 1248–49.

Similarly, the sale of a product specifically labeled for use in a patented method constitutes *inducement* to infringe that patent. *See Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed.Cir.2010) (finding intent to induce infringement based on the product label authorizing the patented use, which "would inevitably lead some consumers to practice the claimed method." (emphasis added)). Indeed, "the substantive determination whether actual infringement or inducement will take place is determined by traditional patent infringement analysis, just the same as it is in other infringement suits, including those in a non-ANDA context, the only difference being that the inquiries now are hypothetical because the allegedly infringing product has not yet been marketed." *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365-66 (Fed. Cir. 2003). This is because "pharmaceutical companies do not generally treat diseases; rather, they sell drugs to wholesalers or pharmacists, who in turn sell the drugs to patients possessing prescriptions from physicians. Pharmaceutical companies also occasionally give samples of drugs to doctors and hospitals. In none of these cases, however, does the company itself treat the disease." *Id.* at 1363. With this framework in mind, the Court analyzes infringement of the elements of each asserted claim and patent.

A. ’628 Patent

There are two outstanding issues regarding infringement of the ’628 patent. First, Defendants, DRL and Actavis (only), argue that their ANDA products do not infringe Claims 16 and 17 of the ’628 patent because their products do not contain a “buffer.” Second, all Defendants claim that Plaintiffs have failed to meet their burden of proving Defendants’ respective ANDA products infringe the *in vivo* limitations recited in Claim 1 of the ’628 patent. The Court finds Plaintiffs have failed to meet their burden with reference to the former, but have done so successfully regarding the latter.

1. “Buffer”

Claim 1 of the ’628 patent recites “a solid pharmaceutical composition comprising zolpidem or a pharmaceutically acceptable salt thereof . . . , the pharmaceutical composition further comprising a buffer . . . .” (JTX 003 at Claim 1). Claims 2-17 of the ’628 patent, which each depend directly or indirectly upon Claim 1, incorporate by reference all limitations of Claim 1. (Id. at Claims 12-17). The term “buffer,” as used in Claim 1 of the ’628 Patent, means “a buffer system of two or more buffering agents.” (Claim Construction Order, ECF No. 186, at 2). The term "buffering agent," is construed to mean "a proton-donating component or proton-accepting component used to maintain and/or achieve an approximate pH range.” (Id.). It is undisputed that Novel’s ANDA product contains a buffer system of two or more buffering agents and therefore, this analysis shall apply to Defendants, Actavis and DRL, alone.

The first buffering agent in Actavis’ ANDA product is [redacted] a pH-adjusting agent, as admitted by Actavis’ formulation expert Dr. Banakar. (Tr. 4.136:1-3 (Banakar)). Plaintiffs assert that Actavis infringes Claims 16 and 17 of the ’628 patent, because Actavis’ ANDA products

contain [redacted] in addition to tartaric acid, as a second buffering agent. (*See* Tr. at 3.107:17-3.108:25, 4.12:10-24, 4.15:16-23 (Polli)). Similarly, DRL's first buffering agent is [redacted], which is listed on its ANDA product as a pH-modifier. While DRL appeared to dispute at trial whether [redacted] is in fact a buffering agent, DRL had previously characterized [redacted] as a buffering agent in its non-infringement contentions. (Tr. 5.34:15–5.36:21 (McConville)). This admission taken in conjunction with DRL's senior director of formulations, Dr. Viswanathan's testimony, stating that [redacted] is used in DRL's ANDA Product to "increase [pH] beyond 8.2 . . . and ensure that it doesn't come below that 8.2," confirms that [redacted] is used to achieve and maintain an alkaline pH range. (Tr. 4.65:1–7 (Viswanathan); *see also* Tr. 4.60:17–20). As construed, a "buffering agent" performs this function and therefore the Court concludes [redacted] is in fact a buffering agent. Plaintiffs assert that DRL infringes Claims 16 and 17 of the '628 patent, because DRL's ANDA products contain [redacted] *and tartrate* as buffering agents used to achieve and maintain pH to facilitate the transmucosal delivery of zolpidem. (PFOF ¶579). However, based upon the evidence and for the reasons that follow, the Court finds that Plaintiffs have failed to prove by a preponderance of the evidence that Actavis' and DRL's ANDA products contain a *second* buffering agent, neither as tartaric acid nor tartrate.

a. Tartrate cannot exist as a single chemical entity and zolpidem tartrate is not a buffering agent.

At trial, Defendants' expert, Dr. McConville, testified in great detail about the structure of zolpidem tartrate and why tartrate could not be removed from its bond with zolpidem to then become a single buffering agent. The Court finds this reasoning persuasive. That is, zolpidem tartrate is a salt containing a stoichiometric amount of two molecules of zolpidem cation per one

tartrate anion. (Tr. 4.189:4-4.190:13 (McConville)). Dr. McConville explained that a salt, such as zolpidem tartrate, is a neutral compound consisting of a positively charged cation and a negatively charged anion where the cation and anion are ionically bound (or attracted to one another), forming one of the strongest bonds in chemistry. (Tr. 4.170:10-23 (McConville)). It was also explained by Dr. Banakar, that tartrate cannot exist as a single chemical entity because it is a charged negative compound, and thus no portion of zolpidem can separate from the tartrate in the mouth. (Tr. 4.124:21-24 (Banakar)).

Dr. Banakar, in his testimony, explained further to the Court how a buffer works and why zolpidem tartrate could not provide assistance to this function and therefore, is not a "buffering agent." That is, in order for a buffer to work, there has to be a conjugate acid for the base. (Tr. 4.125:12-23. (Banakar)). A "proton-donating component" is an acid and a "proton-accepting component" is a base. (Tr. 4.168:14-19 (McConville)). Dr. Banakar then explained zolpidem tartrate is a neutral compound (neither acidic or basic) and thus neutral compounds are neither proton-donating nor proton-accepting as required by the construction of "buffering agent." (Tr. 4.120:4-7 (Banakar)). In sum, because the Court is persuaded by the evidence that zolpidem tartrate is neutral, and thus unable to form a buffer with [redacted] for example, a base, the tartrate cannot be characterized as a buffering agent.

b. Zolpidem Tartrate in Actavis' and DRL's ANDA products is a single compound which does not contain tartaric acid.

At trial, Plaintiffs presented evidence through their expert, Dr. Polli, that because the tartrate component of zolpidem tartrate comes from tartaric acid, it donates a proton to the compound and therefore is proton-donating under the Court's construction of "buffering agent." (Tr. 3.73:133-3.74:12 (Polli)). Dr. Polli supported this proposition by pointing to the USAN, the

committee that gives drugs name in the United States, who characterizes tartaric acid as a buffering agent in pharmaceutics. (Tr. 3.72:21–3.73:12 (Polli); PTX 450 at PLSEXP404). However, Defendants do not challenge whether or not tartaric acid may in some cases act as a buffering agent, but rather whether tartaric acid is present at all in Defendants' ANDA products. Indeed, the Court finds there was sufficient evidence at trial to refute Plaintiffs' assertion that tartaric acid exists in DRL or Actavis' ANDA products.

Dr. McConville's testimony exemplified that there is no tartaric acid in either DRL's or Actavis' ANDA products through his explanation of zolpidem tartrate and polymorphism. (Tr. 4.186:6-7 (McConville); DTX 1001). Polymorphism exists when a compound or material exists in distinct crystalline forms or types, known as "polymorphs," each of which can be can be distinguished from other polymorphs using known methods such as powder X-Ray Diffraction. (Tr. 4.185:25-4.186:5; 5.14:18-5.17:6 (McConville); DTX 1001). According to Dr. McConville, analytical studies using X-ray diffraction and thermal analysis of [redacted] of zolpidem tartrate—the polymorph used in Actavis' and DRL's ANDA products—demonstrate that zolpidem tartrate does not contain tartaric acid. (*See* Tr. 4.185:19-4, 186:14, 5.17:1-5.18:3, 5.21:6-16 (McConville); PTX 55). Plaintiffs have not credibly refuted this analysis and therefore the Court is unconvinced by a preponderance of the credible evidence, that tartaric acid is present. Consequently, tartrate, in the Court's view, is not characterized as the second buffering agent in either DRL or Actavis' ANDA products.

c. The language of Claim 1 indicates that the active pharmaceutical ingredient and "buffer" are intended be two distinct and separate components of the claimed solid pharmaceutical composition.

Claim 1 of the '628 patent provides a "method for treating insomnia, comprising the steps of: administering a solid pharmaceutical composition comprising zolpidem or a pharmaceutically

acceptable salt thereof to a subject prone to insomnia, the pharmaceutical composition further comprising a buffer." After a review of the evidence at trial, the Court finds that the claim delineates that *in addition to zolpidem tartrate*, there must be two buffering agents in an ANDA product for it to infringe the '628 patent, therefore eliminating the possibility that tartrate can be categorized as a buffering agent in the composition.

The phrase "further comprising" signals that these claimed elements ("zolpidem or a pharmaceutically acceptable salt thereof," on the one hand, and "a buffer" on the other) are distinct components of the solid pharmaceutical composition. *See HTC Corp. v. IP Com GmbH & Co.*, 667 F.3d 1270, 1275 (Fed. Cir. 2012) ("[F]urther comprising" signals something "additional."); *Remediation Prods., Inc. v. Adventus Ams., Inc.*, 3:07-cv-153-RJC, 2009 WL 57456 (W.D.N.C. Jan. 7, 2009) ("The construction of the phrase 'further comprising' includes additional recited elements."). Dr. Banakar opines that this reading—where one ingredient cannot serve more than one purpose in the same composition—aligns with the FDA and regulatory agencies around the world requiring "that a single ingredient serve one function in any given composition." (Tr. 4.128:20-4.130:18 (Banakar)). Indeed, Intermezzo® which encompasses the '628 patent, further verifies individualized functions as Intermezzo® explicitly contains zolpidem tartrate in addition to two buffering agents (sodium carbonate and sodium bicarbonate). (*See* e.g. Tr.4.123:4-7 (Banakar)). Even if the Court had construed tartrate and/or tartaric acid to be a buffering agent, Plaintiffs have not established by a preponderance of the credible evidence that tartrate, a part of the pharmaceutically acceptable salt, was intended to serve dual functions in the claim. The Court therefore concludes that each listed function of the ingredients in the ANDA products are the sole functions. Thus, the single function of zolpidem tartrate in Actavis' and DRL's ANDA products is as listed, the active pharmaceutical ingredient. The single function of [redacted] in Actavis'

ANDA products is therefore a pH-adjusting agent. And finally, the single function of [redacted] in DRL's ANDA products is as listed, a pH modifier. DRL and Actavis' ANDA products each contain just one buffering agent.

For the reasons set forth above, the Court determines that substantial evidence supports that DRL and Actavis' ANDA products each contain only one buffering agent and that Plaintiffs have not come forth with sufficient credible evidence to establish infringement of the '628 patent by a preponderance of the evidence. Having concluded that Defendants, DRL and Actavis ANDA products, if sold, would not infringe Claim 1 of the '628 patent, the Court further concludes that these ANDA products would also not infringe Claims 16 and 17, which depend from Claim 1.

2. The *in vivo* claim limitations of the '628 patent.[6]

Defendants assert that Plaintiffs have failed to prove by a preponderance of the evidence that two limitations of the '628 patent are infringed by Defendants' ANDA products. Defendants therefore maintain that Claims 9, 16 and 17 of the '628 patent are not infringed. Defendants take issue with the limitation that the buffer "raises the pH of saliva to a pH of about 7.8 of greater" and requirement that the solid pharmaceutical composition "dissolves within about 10 minutes or less within the oral cavity following administration." (JTX-002 at Claim 1). Defendants' argument, in sum, provides that Plaintiffs cannot rely on *in vitro* data to establish infringement of the *in vivo* claim limitations articulated above. For this proposition, Defendants rely almost exclusively on *Alza Corp. v. Mylan Laboratories, Inc.* 388 F.Supp. 2d 717, 725 (N.D. W. Va. 2005) *aff'd* 464 F.3d 1286 (Fed Cir. 2006). As set forth below, the Court does not agree with

[6] The Court hereby incorporates this Section into its later analysis of the *in vivo* limitations of the '809 patent.

Defendants' interpretation of *Alza Corp.*, as it relates to the facts of the case at bar and finds sufficient evidence of infringement of the *in vivo* limitations of the '628 patent. Defendants[7], therefore, are found to have infringed Claims 9, 16 and 17 of the '628 patent in this regard.

a. *Alza Corp. v. Mylan Laboratories, Inc.*

The *Alza Corp.*, litigation arose from Defendants' filings of ANDAs for once-daily, controlled-release oxybutynin formulations. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1288 (Fed. Cir. 2006). Oxybutynin is a drug used to treat urinary incontinence. Once-a-day dosing provides the usual benefits of convenience, steady-dosing, and in addition, possibly reduced absorption of a metabolite that leads to side-effects. *Id.* Claim 2 of the '355 patent was at issue and stated:

> A sustained-release oxybutynin formulation for oral administration to a patient in need of treatment for urge incontinence comprising a therapeutic dose of an oxybutynin selected from the group consisting of oxybutynin and its pharmaceutically acceptable salt that *delivers* from 0 to 1 mg in 0 to 4 hours, from 1 mg to 2.5 mg in 0 to 8 hours, from 2.75 to 4.25 mg in 0 to 14 hours, and 3.75 mg to 5 mg in 0 to 24 hours for treating urge incontinence in the patient.

Id. at 1289 (emphasis in original). The district court construed the '355 patent claims in its *Markman* Order, construing the word "deliver" to refer to the rate of *in vivo* release in the gastrointestinal ("GI") tract. *Id.*

At trial, Plaintiff, Alza Corp., did not present direct evidence that one Defendants' ANDA formulation released drug in the GI tract at the rates claimed by the '355 patent. *Id.* However, it

[7] Defendants, DRL and Actavis, do not infringe the '628 patent as they do not contain "buffer," but the Court completes its infringement analysis regarding the '628 patent for purposes of Defendant, Novel (as well as TWi and Par if applicable).

did offer two other types of evidence: 1) the rate at which the generic product released oxybutynin in an *in vitro* dissolution apparatus; and 2) the rate at which the ANDA product resulted in the accumulation of oxybutynin in the bloodstream. Ultimately, the district court found that Alza had failed to meet its burden of proof on infringement, stating:

> Alza cannot rely exclusively on *in vitro* test results to prove infringement of *in vivo* release rates. *See Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200 (Fed.Cir.1991) (holding that "the district court erred in accepting the *in vitro* data as support for claim containing what has been found to be an *in vivo* limitation"). Indeed, without reliable *in vivo* data comparing the release rates of the accused product against the claimed ranges of the '355 patent, there can be no finding of infringement—either literally or under the doctrine of equivalents.

Alza Corp. v. Mylan Labs., Inc., 388 F. Supp. 2d 717, 725 (N.D.W. Va. 2005). On September 6, 2006, the Federal Circuit affirmed the ruling of the district court, but made clear why, in the *Alza* case, the *in vitro* data was insufficient. The Federal Circuit explained: "The critical deficiency in the evidence presented by Alza was not that it was 'indirect' rather than 'direct,' but rather that it failed to *credibly link* these pieces of evidence with the relevant pharmacokinetic parameter—the rate of *in vivo* dissolution in the GI tract." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1296 (Fed. Cir. 2006) (emphasis added). That is, because "the obtained *in vitro* dissolution rates vary widely with the choice of experimental parameters," the Federal Circuit found that "Alza's evidence of *in vitro* dissolution rates [was] irrelevant absent evidence demonstrating that the *in vitro* system is a good model of actual *in vivo* behavior." *Id.* at 1297.

Defendants in the present case, read the *Alza Corp.*, litigation to stand for the proposition that *in vivo* claim limitations can only be infringed upon conduction of *in vivo* testing. The Court disagrees. *In vitro* testing is suitable to prove *in vivo* claim limitations if there is *a credible link* between the *in vitro* data and *in vivo* data. In other words, without affront to the Federal Circuit

holding in *Alza Corp.*, infringement can be found based on *in vitro* data where the evidence demonstrates that the *in vitro* system adequately modeled the results that would be derived from *in vivo* conditions. *Allergan, Inc. v. Watson Labs., Inc.-Florida*, 869 F. Supp. 2d 456, 500 (D. Del.) aff'd, 470 F. App'x 903 (Fed. Cir. 2012). Because the Court finds (and explains below) that at trial, Plaintiffs presented evidence of *in vivo* limitations via Defendants' ANDA data and *in vitro* dissolution data which was then considered in combination with the inventor's prosecution declaration, the known information of dissolution rates and *in vivo* data from Intermezzo®, Plaintiffs have met their burden by linking the *in vitro* and *in vivo* data. Accordingly, Defendants are found to infringe the *in vivo* limitations of the '628 patent.[8]

b. Plaintiffs' evidence, *in vitro* and otherwise, of infringement.

i. "[R]aises the pH of saliva to a pH of about 7.8 of greater."

Defendants argue, in the main, that Plaintiffs have failed to show their products meet the "raises the pH of saliva to a pH of about 7.8 of greater" element of the asserted claims because the dissolution testing results (i.e. the *in vitro* data) does not sufficiently model *in vivo* conditions of the mouth. Defendants cite a number of propositions in support of this contention. First, Defendants assert that simulated saliva does not adequately mimic saliva and therefore pH must be measured in natural human saliva. (Tr. 2.231:4-2:232:11 (Garegnani), 6.41:6-14 (Michniak-Kohn)). Second, Defendants attempt to discredit dissolution test results by reasoning that depending on which simulated saliva recipe one chooses, pH measurements will fluctuate, sometimes dramatically. (DTX 291 at 1109; Tr. 6.61:5-11 (Michniak-Kohn)). Lastly, Defendants point the Court to the fact that Plaintiffs did not conduct any *in vivo* testing on Defendants' ANDA

[8] Such an analysis also applies equally to the '809 patent where appropriate.

products. After a thorough consideration of the totality of the evidence presented, the Court finds Defendants' position unpersuasive and disagrees with the contention that Plaintiffs, via Dr. Polli's testimony, have failed to show that it is more likely than not that Defendants' proposed products "raise[] the pH of saliva to a pH of about 7.8 of greater."

At trial, Plaintiffs presented evidence that each Defendants' product would raise the pH of saliva to a pH of about 7.8 of greater. First, Plaintiffs offered evidence that each Defendant has represented to the FDA the specific effect each product has on the pH of saliva. DRL informs FDA that it's "[redacted]" (PTX 98R at DRL0001294; Tr. 3.66:4–23 (Polli)). Actavis' ANDA specifies that "[redacted]" (PTX 55 at ACT-ZOL-0000275; Tr. 3.103:10–22 (Polli)). Novel's ANDA tells FDA that "[t]he amounts of sodium bicarbonate and sodium carbonate [in Novel's product] were also challenged and optimized based on the drug product target pH," which it indicated to be "a pH above 9." (PTX 138 at NOVZ0007909; Tr. 3.58:7–25, 3:59:17–3.60:6 (Polli)). Next, Plaintiffs offered Defendants' ANDAs that report *in vitro* pH testing data to substantiate their statements to the FDA about the pH levels. The pH achieved in this *in vitro* testing (above 9.5 for all Defendants) far surpasses the minimum bar of at least 7.8 for this required pH level limitation. Specifically, Novel's testing produced a pH of 9.56 in simulated saliva; DRL's testing produced pH values as high as [redacted] in simulated saliva; and Actavis' testing produced a pH of [redacted] in deionized water. (Tr. 3.58:7–3.60:19; 3.91:6–3.94:16, 3.109:21–3.111:4 (Polli)). This data, when properly linked to the *in vivo* limitation, fully supports a finding of infringement.

Plaintiffs also provided the Court with the patent inventor's prosecution declaration. Said declaration expressly instructs that *in vitro* measurements in simulated saliva (Novel, DRL) or deionized water (Actavis) are appropriate to establish the *in vivo* pH claim element. Dr. Singh, the inventor, used pH testing in deionized water and simulated saliva to successfully persuade the USPTO that the prior art did not "raise[] the pH of saliva to a pH of about 7.8 or greater." (JTX 6 at TRANSIZ00059306–14; *id.* at TRANSIZ00059338–41) (*See also* Pls.' FOF ¶¶ 461–62, 569–70, 600–01). Dr. Polli explained that this is indicative of how the patent office was "inspired by the experiments … such the simulated saliva allows one to differentiate whether a formulation is within that claim limitation or outside." (Tr. 3.89:19-22 (Polli)). Indeed, this is further confirmed by Mr. Gorlamari, Novel's former formulation scientist that developed its ANDA product, who testified that "we can't get the actual saliva, so, usually, we typically get a simulated saliva," and that, based on his experience in the pharmaceutical industry, the simulated saliva Novel used "should be equivalent to the saliva" in a subject's mouth for purposes of pH testing. (Tr. 3:11:8–3.12:4 (Gorlamari)). Mr. Garegnani, Novel's corporate 30(b)(6) witness on the development and formulation of Novel's ANDA products, also acknowledged that simulated saliva, including the volume Novel used to run its pH testing, was used to approximate actual saliva in the mouth. (Tr. 2.232:22–2.233:13 (Garegnani)). This is precisely the breed of credible "link" that the *Alza Corp* litigation approved. Here, the *in vitro* testing is authenticated by numerous sources to be "a good model of actual *in vivo* behavior." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1297 (Fed. Cir. 2006).

With respect to simulated saliva criticisms of Defendants' expert, Dr. Michniak-Kohn, who claimed that there are too many different formulations that can be used with differing results, even she acknowledged that actual saliva varies person to person and can even vary for the same person

at different times of the day. (Tr. 6.56:3–24, 7.25:11–16 (Michniak-Kohn)). Therefore, differing formulations are actually representative of differing conditions in the mouth from person to person. Admittedly, saliva is 99% water, and simulated salivas "have compositions[] which are more or less the same as that of natural saliva." (Tr. 7.25:11–7.26:1, 7.24:4–10 (Michniak-Kohn), DTX 291). As a result, the Court grants this critique only limited credibility. However, of more practical importance, it would be difficult to imagine an *in vivo* test to gain the data Defendants request. Throughout trial, Defendants have persistently criticized Plaintiffs for failing to test Defendants' respective ANDA products. However, the Court will not overlook the implications of such unapproved testing. Indeed, it would be highly unethical to have testing performed on humans (*i.e. in vivo*) for unapproved products particularly for the limited purpose of patent litigation as Defendants' appear to suggest. *Allergan, Inc. v. Watson Labs., Inc.–Fla.*, 869 F. Supp. 2d 456, 500 (D. Del. 2012) ("[T]esting defendants' unapproved products in live human subjects is neither feasible nor ethical.").[9] For both this reason and those articulated above, the *in vitro* data is credibly and sufficiently linked to other credible evidence presented to prove infringement by a preponderance of the evidence for the claim limitation "raises the pH of saliva to a pH of about 7.8 of greater."

ii. "[W]herein the solid pharmaceutical composition dissolves within about 10 minutes or less within the oral cavity following administration."

The majority of Defendants' arguments related to the claim limitation "wherein the solid

[9] *See also Zenith Labs. Inc. v. Bristol-Myers Squibb Co.*, No. 91-3423, 1992 WL 340761, at *18 (D.N.J. Aug. 6, 1992) ("[I]n vivo experimentation could not be justified under medical ethics constraints merely to prove patent infringement."), *rev'd on other grounds*, 19 F.3d 1418 (Fed. Cir. 1994).

pharmaceutical composition dissolves within about 10 minutes or less within the oral cavity following administration" revolves around the element "oral cavity." Defendants essentially argue that dissolution of the composition, for purposes of infringement, must be measured in the oral cavity. Defendants note the differences between USP disintegration tests and conditions within the oral cavity in support of this proposition. The Court finds however, as set forth below, that based on the credible evidence presented at trial, Plaintiffs have met their burden of proving infringement of this "oral cavity" *in vivo* element of the '628 patent.

Plaintiffs provided the Court with each of Defendants' ANDA's USP test results, which all reflect a showing of at least [redacted] dissolution within 10 minutes or less. (*See* PTX 121, PTX 67, PTX 102). This is undisputed. To link these results to the oral cavity, Plaintiffs offered evidence that each of Defendants' ANDA products indicate that they were designed for [redacted] all of which are qualities a POSA would anticipate for dissolution in the oral cavity. (*See* PTX 121, PTX 55, PTX 97). Additionally, Plaintiffs provided that both the '628 patent itself, as well as the standard practice in the pharmaceutical industry, specify that *in vitro* USP dissolution data is appropriate to measure *in vivo* dissolution. On cross-examination, Dr. Polli explained how those of skill in the art rely on USP *in vitro* testing as a surrogate for *in vivo* testing, stating:

> I don't know of a way to measure dissolution in the mouth. I don't know anybody that does. That would be extremely unusual. And then when I read the patent, I see what I would have expected, USP dissolution testing, so it kind of confirms what I would have expected anyway.

(Tr. 3.151:8–24 (Polli)). The specification of the '628 Patent further corroborates Dr. Polli's opinion and defines *in vitro* USP tests as suitable for determining the extent to which a solid dosage

form (*e.g.*, Defendants' ANDA Products) dissolves in a patient's mouth (*i.e.*, *in vivo*). Under the claimed inventions:

> The terms "disintegration" and "dissolution" are used interchangeably to refer to the reduction of a solid dosage form of the present invention to a liquid form. More particularly, a *complete disintegration or dissolution* of a solid dosage form *refers to less than about 25% by weight of the solid dosage form remaining in the mouth* following an appropriate time period, e.g., 5 minutes or less, after administration. . . . *Suitable methods known in the art for determining the dissolution profile of a solid dosage form include, e.g., USP dissolution tests* such as USP <711> Apparatus 1 or USP <711> Apparatus 2.

(JTX 3 at 6:38–51 (emphases added)).

While Defendants appear to take issue with the volume ([redacted]) and paddle speed ([redacted]) parameters used in their own tests, Dr. Polli testified on cross-examination that these parameters are commonly used to make sure that the tests are not only related to *in vivo* performance but are also reproducible, a point that this Court finds credible. (Tr. 3.149:7–3.150:13 (Polli)). Dr. Polli explained that these tests are "intended to mimic what goes on in the mouth." (Tr. 3.148:6–12 (Polli)). Indeed, Defendants conducted *in vitro* USP tests using the same parameters, including the approximate pH [redacted] and temperature [redacted] of the oral cavity. (PTX 102). [redacted] (Tr. 3.96:23–3.99:1 (Polli); *See e.g.* PTX 99). The preponderance of the evidence thus weighs in favor of infringement of the *in vivo* claim limitation "wherein the solid pharmaceutical composition dissolves within about 10 minutes or less within the oral cavity following administration."

3. Remaining Uncontested Infringement Evidence

Beyond the elements discussed *supra* or within this Court's analysis of the '809 patent, and for purposes of completeness, the Court addresses the undisputed elements of the claims asserted against Novel, and finds that Plaintiffs have proven infringement by a preponderance of the evidence. First, with reference to independent Claim 1 of the '628 patent, administering Novel's ANDA Product according to their proposed labeling comprises a method of treating insomnia. (Kryger Tr. 1.245:19–1.246:8; PTX 50 at NOVZ00007869). Further, Novel's ANDA Product according to this label includes administering a solid pharmaceutical composition comprising zolpidem or a pharmaceutically acceptable salt thereof to a subject prone to insomnia under Claim 1 of the '628 Patent. (Kryger Tr. 1.246:9–1.247:17; PTX 50 at NOVZ00007869). Zolpidem is also absorbed across a permeable membrane of the subject's oral mucosa under Claim 1 of the '628 Patent after administration according to Novel's proposed labeling. (Tr. 2.155:13–2.176:4 (Drover)). Thus, the remaining elements of Claim 1 are found to be infringing.

Novel's ANDA Product contains zolpidem or a pharmaceutically acceptable salt thereof in an amount from about 1 mg to about 5 mg, under Claim 16 of the '628 Patent, and in an amount from about 2 mg to about 5 mg, under Claim 17 of the '628 Patent. (Kryger Tr. 1.247:15–1.249:16; Polli Tr. 3.63:2–12; PTX 50 at NOVZ00007869). Novel did not present any evidence to the contrary to dispute this. Sodium bicarbonate and sodium carbonate in Novel's ANDA product also constitute a "buffer" under Claim 1 of the '628 Patent for the same reasons that these components constitute a "binary buffer system" under Claim 22 of the '809 Patent (*see analysis below*). (Tr. 3.117:6–3.117:21 (Polli)). That is, because the sodium bicarbonate and sodium carbonate satisfy the "binary buffer system" element of the '809 patent, they necessarily satisfy the broader "buffer" element. Moreover, the '628 Patent explicitly identifies buffers using sodium

bicarbonate and sodium carbonate, like those in Novel's ANDA product, as preferred embodiments of the invention. (Tr. 3.117:22–3.118:17 (Polli)). As sodium carbonate is a "carbonate buffer," and sodium bicarbonate, a "bicarbonate buffer," Novel's ANDA product indisputably contains the "carbonate buffer" and "bicarbonate buffer" required under the additional asserted claim, Claim 9, of the '628 Patent. (Tr. 3.119:10–18; PTX 138 (Polli)). Novel therefore infringes all remaining claims and elements of the '628 patent.

B. '809 Patent

Plaintiffs assert that Claims 11, 17, and 18 of the '809 patent are infringed by Novel and DRL only. Additionally, Plaintiffs claim that Novel infringes Claim 22 of the '809 patent. This Court previously granted Plaintiffs' Rule 52 motion that Novel infringes Claims 11, 17, and 18, therefore isolating this Court's infringement analysis to Claim 22. (ECF No. 366 at 4). Similarly, DRL challenges its infringement of the '809 patent only as to the "appropriate patient population" element of (independent) Claim 1.[10]

1. Novel Infringes Claim 22 of the '809 Patent.

Novel contested infringement of Claim 22 of the '809 patent only with respect to the "pH of said subject's saliva" limitation. The Court incorporates by reference Section A., 2., b., i., of this Opinion (finding "the *in vitro* data is credibly linked to other evidence to prove infringement

[10] For reference, Claim 1 of the '809 patent recites: A solid unit dosage composition for the treatment of MOTN insomnia, said composition comprising an effective amount of zolpidem or a salt thereof, formulated for delivery of zolpidem across a subject's oral mucosa, wherein said effective amount is an amount of less than 1.30 x 10-5 moles of zolpidem, and between about 25 ng/mL and about 50 ng/mL within 20 minutes of administration, when evaluated *in an appropriate patient population*. (JTX 002)(emphasis added).

by a preponderance of the evidence for the claim limitation [‘]raises the pH of saliva to a pH of about 7.8 of greater.[’’’]). For purposes of completeness, the Court provides additional relevant evidence to Novel only, which demonstrates Plaintiffs have proved Novel infringes Claim 22 of the ’809 patent.

The face of the ’809 patent indicates that the preferred embodiment of the invention includes a binary buffer system comprising sodium bicarbonate and sodium carbonate—the same system as in Novel’s ANDA Product. (Tr. 3.50:18–3.52:4 (Polli); JTX 2 at 28:37–39). Sodium carbonate is a proton-accepting component and sodium bicarbonate is a proton donating component. (Tr. 3.51:6-17 (Polli)). Further, Dr. Polli opines that the weight ratio of sodium carbonate and sodium carbonate in Novel’s ANDA product—2.3 to 1—falls within the preferred ranges taught in the ’809 Patent to raise the pH of saliva above about 8.5. (Tr. 3.52:5–3.54:3; JTX 2 at 27:37–57, 28:46–48 (Polli)). Additionally Dr. Polli points to the pKa values of carbonate and sodium bicarbonate to confirm the teachings of the ’809 of achieving and maintaining a pH range above 8.5. (Tr. 3.55:21–3.56:13, 3:57:18–3.58:6 (Polli)). Finally, it is undisputed that Novel conducted pH testing in simulated saliva, and reported in its ANDA that the amounts of sodium carbonate and sodium bicarbonate in its final ANDA Product achieved a pH of 9.56. (Tr. 3.60:7–23; Stip. Facts ¶¶ 215–22 (Polli)). For these reasons and the corresponding findings articulated in Section A., 2., b., i., of this Opinion, Novel is found to infringe Claim 22 of the ’809 patent as its ANDA product contains a system used to “maintain and/or achieve an approximate pH range comprising at least one proton-donating component and at least one proton accepting component,” as required by the construction of Claim 22’s “binary buffer system.”

2. DRL Infringes the "appropriate patient population" element of the '809 patent.

Plaintiffs assert that DRL infringes Claims 11, 17 and 18 of the '809 patent where Claim 11 depends from Claim 1 and Claims 17 and 18 are multiple dependent claims. DRL contests infringement as to Claim 1 of the '809 patent only. Independent Claim 1 of the '809 patent states in relevant part:

> A solid unit dosage composition for the treatment of MOTN insomnia, said composition comprising an effective amount of zolpidem or salt thereof … sufficient to produce a plasma concentration between 25 ng/ml and about 50 ng/ml within 20 minutes of administration, when evaluated in *an appropriate patient population.*

(JTX 002) (emphasis added). DRL argues that Plaintiffs failed to prove their ANDA product infringes this patent because DRL's ANDA product does not meet the required plasma concentration at 20 minutes when evaluated in an "appropriate patient population." DRL first opposed this element during the summary judgment phase of litigation. That is, the "appropriate patient population" element was not disclosed through DRL's non-infringement contentions, which only disputed Claim 5 of the '809 patent. (Opinion, ECF No. 325 at 26). Pursuant to Local Patent Rule 3.7, leave to amend infringement contentions may be granted "by order of the Court upon a timely application and showing of good cause." DRL never sought leave to amend its non-infringement contentions to reflect the arguments it made regarding the "appropriate patient population" element. Therefore, the Court ordered that DRL would "not be permitted to offer new evidence of non-infringement regarding the claim limitation 'appropriate patient population,' but shall only rebut the sufficiency of Plaintiffs' evidence of infringement of this claim." (Order, ECF No. 331 at n. 1). With this in mind, the Court evaluates the sufficiency of Plaintiffs' evidence and finds DRL has infringed this element.

At trial Plaintiffs pointed the Court to DRL's bioequivalence study and the expert testimony of Dr. Drover for the majority of its evidence relating to DRL's ANDA product meeting the required plasma concentration at 20 minutes when evaluated in an "appropriate patient population." DRL commissioned a clinical trial to determine whether its ANDA Product is bioequivalent to Intermezzo®. (PTX 101). In the clinical trial, which DRL submitted to FDA as part of its ANDA filing, DRL's 3.5 mg ANDA Product was administered to 56 subjects. (*Id.* at DRL0003800; Tr. 2.185:13–23 (Drover)). Blood was taken from each subject at multiple points in time, including at 20 minutes after administration where each of the blood samples was then analyzed to determine the subject's zolpidem plasma concentration. (PTX 101 at DRL0003791). The clinical study report includes all of the raw data from the study, as well as the statistical analysis of that data. According to the report, the average plasma concentration at 20 minutes after administration was 34.46 ng/mL, which is within the claimed range of "between about 25 ng/mL and about 50 ng/mL." (PTX 101 at DRL0004169; Tr. 2.187:1–21 (Drover)).

The '809 Patent defines an "appropriate patient population" to include "a patient population used for a clinical study." (JTX 2 at 10:1–5). Dr. Drover explained that the study population used in DRL's bioequivalence study, a clinical trial, was typical of that used in other clinical trials. (Tr. 2.185:13–2.186:25 (Drover)). This study population consisted of 13 men and 43 women, ages 20 to 65 who were chosen on the basis of various inclusion and exclusion criteria specified in the study report. (PTX 101 at DRL0003784–86). The study subjects were chosen on the basis of (among other things) their age, weight, and ability to metabolize zolpidem—all of which the '809 Patent expressly identifies as being relevant factors in constructing an appropriate patient population. (JTX 002 at 10:1–5; PTX 101 at DRL0003784–86; Tr. 2.185:21–2.186:4

(Drover)). Dr. Drover further explained that these criteria were also typical of those used in clinical trials.

There is no evidence before the Court that the '809 Patent requires that men and women be segregated into separate patient populations as DRL would lead it to believe. (Tr. 2.191:18–21 (Drover)). The '809 patent lists a number of factors that can be considered in assembling an appropriate patient population, including "age, weight, the number of hours of time in bed remaining, and/or the ability of a subject to metabolize zolpidem." (JTX 2 at 10:1–5). Notably, the patent does not include gender as one of the exemplary inclusion or exclusion criteria, and thus indicating that a mixed-gender population is appropriate. (Id.). Dr. Drover explained that even though the study population for DRL's bioequivalence study included both men and women, it was still conducted in an "appropriate patient population," because even with women included, the inclusion and exclusion criteria used for the study were typical and similar to those previously used in published zolpidem studies. (Tr. 2.190:18–25 (Drover)). In light of the aforementioned, and particularly highlighting the guidance of the '809 patent itself, DRL's contention that its bioequivalence study was not conducted on an "appropriate patient population" because it included both men and women is unconvincing to the Court.

Similarly, the fact that DRL's bioequivalence study included one elderly subject does not overcome the conclusion that the study was performed on an appropriate patient population and therefore preclude DRL from infringement of this element. (Tr. 2.188:7–10 (Drover)). The reported 20-minute concentration for the one elderly subject was close to the study population's average. (Tr. 2.189:24–2.190:4 (Drover)). Thus, the elderly subject did not alter Dr. Drover's opinion that the study was performed in an "appropriate patient population" because the reported concentration did not meaningfully change the average 20 minute plasma concentration, even

though the subject, because she was elderly, is expected to exhibit higher plasma concentrations than a non-elderly subject. (Tr. 2.188:7–10, 2.189:4–2.190:7 (Drover)). Even assuming *arguendo* that the elderly and non-elderly should be considered separate patient populations, Dr. Drover calculated that, if the one elderly subject were removed from the study, the average plasma concentration 20-minutes after administration would be 34.3 ng/mL, which is still between the delineated range of "about 25 ng/mL and about 50 ng/mL," according to the '809 patent. (Tr. 2.188:7–10, 2.189:4–2.190:7 (Drover)). DRL's bioequivalence study, when taken in conjunction with Dr. Drover's testimony, establishes that DRL's tablets contain an effective amount of zolpidem that is "sufficient to produce a plasma concentration between about 25 ng/mL and about 50 ng/mL within 20 minutes of administration, when evaluated in an appropriate patient population."

3. Remaining Uncontested Infringement Evidence

Although Defendant, DRL, did not dispute infringement as to the remaining elements of Claim 1 nor Claims 11, 17, 18, the Court addresses whether Plaintiffs have met there burden of proving infringement. Likewise, Claim 22 of the '809 patent was asserted against Novel and found by the Court to be infringed. However, because asserted Claim 22 depends from independent Claim 12 of the '809 patent. The Court must determine if Claim 12 is also infringed. The findings below establish that Plaintiffs have met their burden of proving these Claims and elements are infringed by DRL and Novel by a preponderance of the evidence.

a. DRL Infringes Claim 1 of the '809 Patent

Asserted Claims 11, 17, and 18 depend from independent Claim 1. (JTX 002, Claims 1, 11, 17, 18). DRL's proposed label establishes the majority of the relevant claim elements. The first element of claim 1, "[a] solid unit dosage composition for the treatment of MOTN insomnia" is found in the "Indication and Usage" section of the label, stating that DRL's ANDA product comprises "tablets . . . indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep." (PTX 48 at DRL0000783; Tr. 1.237:10–1.238:4 (Kryger)). A "tablet" is "a solid unit dosage composition," and the indication shows that the tablets will be used "for the treatment of MOTN insomnia." (Tr. 1.237:10–1.238:4 (Kryger)). DRL's proposed label also establishes that its ANDA Product satisfies the second element of Claim 1, requiring that "said composition compris[e] an effective amount of zolpidem or a salt thereof[.]" (JTX 002, Claim 1). The Court construed "effective amount of zolpidem" to mean "amount of zolpidem that is capable of achieving a therapeutic effect in a subject in need thereof." (Order, ECF No. 186 at 2). Dr. Kryger explained that a POSA would understand the "therapeutic effect" to be efficacy in treating MOTN insomnia. (Tr. 1.238:23–1.239:3 (Kryger)). DRL's proposed label reports the results of a sleep laboratory study: "Doses of 3.5 mg and 1.75 mg zolpidem tartrate [*i.e.*, DRL's ANDA Product] significantly decreased both objective and subjective sleep latency after a scheduled middle-of-the-night awakening as compared to placebo," and the results of an outpatient study: "Subjective (patient-estimated) time to fall back to sleep after middle-of-the-night awakening was significantly shorter for zolpidem tartrate 3.5 mg [*i.e.*, DRL's ANDA product] compared to placebo." ((PTX 48 at DRL0000795-96; Tr. 1.239:8–1.240:9 (Kryger)). It was therefore demonstrated at trial that a POSA would read this clinical data to

demonstrate that DRL's ANDA Product has an effective amount of zolpidem to achieve a "therapeutic effect." (Tr. 1.240:10–13 (Kryger)).

The third element of Claim 1, requiring that "said composition . . . [be] formulated for delivery of zolpidem across a subject's oral mucosa," was shown in DRL's proposed label and formulation design choices. A "Guidance for Industry" from FDA indicates that the intended site of absorption for a "sublingual tablet" is the oral cavity. (PTX 206 at PLSEXP0000256.) In its proposed label, DRL refers to its ANDA product as a "sublingual tablet," showing that, under FDA's understanding, DRL's ANDA product is formulated for delivery across the oral mucosa. (PTX 48 at DRL0000781; Tr. 3.42:4–3.44:11 (Polli)). Moreover, the dosing instructions in DRL's proposed label tell a patient to place the product under their tongue, allow it to break apart completely, and then swallow, which also cooreberates transmucosal delivery as this instruction facilitates oral absorption. (PTX 48 at DRL0000806; Tr. 3.44:12–24 (Polli)). Finally, DRL's ANDA product satisfies the fourth element of claim 1, "wherein said effective amount is an amount of less than 1.30 x 10-5 moles of zolpidem," as demonstrated, again, by Dr. Kryger. (Tr. 1.240:17–1.241:13 (Kryger)). DRL's ANDA seeks approval for two dosage forms, one containing 3.5 mg of zolpidem tartrate and the other containing 1.75 mg of zolpidem tartrate. (Stip. Facts ¶ 140; Tr. 1.176:22–1.177:3 (Kryger); PTX 48 at DRL0000781). Dr. Kryger explained that moles and milligrams are two different ways of measuring the amount of zolpidem in the tablet, where 1.30 x 10–5 moles of zolpidem is equal to 4.975 mg. (Tr. 1.241:1–6 (Kryger)). Thus, both dose strengths of DRL's ANDA product contain an amount of zolpidem less than 4.975 mg, and Claim 1 is infringed.

b. DRL Infringes Claims 11, 16 and 17 of the '809 Patent

DRL's ANDA product satisfies the additional element of Claim 11, "wherein the zolpidem is delivered across at least one of the sublingual or buccal mucosa," through its proposed label and bioequivalence study. Specifically, four pieces of evidence regarding DRL's ANDA product—the dosing instructions (directing a patient to put the product under the tongue and allow it to "disintegrate completely"), higher early plasma concentrations than Ambien® (avoid first pass effect), shorter lag time than Ambien®, and higher Cmax than Ambien®—prove that the zolpidem in DRL's ANDA product is delivered across the sublingual mucosa. (Tr. 2.2.169:8–17 (Drover)). This evidence was not rebutted.

Regarding Claims 17 and 18, DRL's ANDA establishes that its ANDA product satisfies the elements of Claims 17 and 18: "containing about 1.75 mg of zolpidem hemitartrate" (JTX 2, claim 17), and "containing about 3.5 mg of zolpidem hemitartrate." (JTX 2, Claim 18). Zolpidem hemitartrate is another name for zolpidem tartrate. (Tr. 4.24:10–13 (Polli); *see also* Tr. 5.13:17–20 (McConville)). DRL's ANDA seeks approval for two dosage forms, one containing 3.5 mg of zolpidem tartrate and the other containing 1.75 mg of zolpidem tartrate. (Stip. Facts ¶ 140; PTX 48 at DRL0000781). The former dosage practices the additional element of Claim 18, and the latter practices the additional element of Claim 17. (Tr. 1.241:7–13 (Kryger)).

c. Novel Infringes Independent Claim 12 of the '809 Patent

Novel's proposed label establishes that its ANDA Product satisfies the first and second elements of Claim 12 for the same reasons DRL infringes Claim 1, as the proposed labels are identical in this regard. (PTX 50 at NOVZ0007870; Tr. 1.237:10–1.238:4, 1.240:10-13(Kryger)).

Novel's ANDA product also satisfies the third element of Claim 12 requiring that **"**said composition . . . [be] formulated for delivery of zolpidem across a subject's oral mucosa," as Novel stipulated that its ANDA product is formulated for delivery across the oral mucosa. (Stip. Facts ¶ 234). The fourth element of Claim 12 requires that "said effective amount is 0.5 to 4.75 mg of zolpidem hemitartrate." (JTX 2, Claim 12). Novel's ANDA infringes this Claim as it seeks approval for two dosage forms, one containing 3.5 mg of zolpidem tartrate and the other containing 1.75 mg of zolpidem tartrate, both of which are between 0.5 and 4.75 mg. (PTX 50 at NOVZ0007869; Tr. 1.243:10–13 (Kryger)).

Finally, the last element of Claim 12 is established by Novel's bioequivalence study, requiring that "said effective amount . . . is an amount sufficient to produce a plasma concentration between about 25 ng/mL and about 50 ng/mL within 20 minutes of administration, when evaluated in an appropriate patient population." Novel commissioned a clinical trial to determine whether its ANDA Product is bioequivalent to Intermezzo®, using an "appropriate patient population," as defined in the '809 Patent. (PTX 139; Tr. 2.181:13–19 (Drover)). In the study, which Novel submitted to FDA as part of its ANDA filing, Novel's 3.5 mg ANDA Product was administered to 36 subjects and blood was then taken from each subject at different points in time, including at 20 minutes after administration. (Tr. 2.181:20–2.182:20 (Drover); PTX 139 at NOVZ0017682). Each of the blood samples was analyzed to determine the subject's zolpidem plasma concentration. (Id.). According to the clinical study report, the average plasma concentration at 20 minutes after administration was 29.268 ng/mL, which is within the claimed range of "between about 25 ng/mL and about 50 ng/mL." (PTX 139 at NOVZ0017704; Tr. 2.181:20–2.182:20 (Drover)). Consequently, Novel's 1.75 mg tablets also contains an effective amount of zolpidem because the pharmacokinetics of zolpidem are linear where a dose reduced by half for the elderly simply

reduces the plasma concentrations by half. (Tr. 1.151:17–25 (Drover); *see also* Tr. 6.112:1–4 (Michniak-Kohn)). Accordingly, an elderly patient that takes Novel's 1.75 mg tablet will have approximately the same blood concentrations as a non-elderly patient taking the 3.5 mg tablet. (Tr. 1.183:19–24 (Drover); *see also* Tr. 6.116:6–10 (Michniak-Kohn)).

C. '131 Patent

Plaintiffs claim all Defendants will induce infringement of Claims 8, 10, 18 and 19 of the '131 patent. Claim 1 of the '131 patent is an independent claim, and therefore Claims 8, 10, 18, and 19 depend therefrom. The only element at issue is the "without residual sedative effects" limitation highlighted below:

> Claim 1: A method of treating middle-of-the night insomnia in a non-elderly patient without prophylactically administering zolpidem, comprising: dosing the patient with a pharmaceutical composition … wherein the pharmaceutical composition permits the patient to awaken at a time about four hours after dosing **without residual sedative effects.**

This Court construed "without residual sedative effects" to mean "with no or minimal subjective feelings of sedation, as evaluated by: (a) testing acceptably in at least one test exploring psychomotor performance, attention, information processing, and memory used by those of skill in the art; and/or (b) demonstrating plasma levels of zolpidem, at an appropriate time point, below about 20 ng/ml." (Opinion, ECF No. 185 at 5-7). It is undisputed that the accused products of Novel, Actavis, and DRL, when tested at four hours after administration, all give zolpidem plasma levels above 20 ng/ml, and therefore Plaintiffs cannot show that "without residual effects" in infringed under prong (b) of this Court's construction. Specifically, the mean plasma concentrations of zolpidem at four hours after the administration of Defendants' ANDA products

were: Actavis' ANDA product yielded [redacted] Novel's ANDA product yielded 25.4037 ng/ml, and DRL's ANDA product yielded [redacted] (PTX 90, PTX 139, PTX 101). Thus the Court's inquiry is limited to whether Plaintiffs have proven, by a preponderance of the evidence, that Defendants' ANDA products would test acceptably in at least one test set forth in part (a) of the Court's construction of the "without residual sedative effects" limitation.

1. *Vermeeren* Driving Study

Each of Defendants' proposed labels includes a section entitled "Driving Study" that reports on the results of a driving performance test conducting on Intermezzo. (Tr. at 1.193:19–22 (Kryger); PTX 46 at ACT-ZOL-0000215; PTX 48 at DRL0000796; PTX 50 at NOVZ0007884.) This is particularly significant as each of Defendants' proposed labels state that "[w]hen you wake up in the morning, be sure that at least 4 hours have passed since you have taken Zolpidem Tartrate Sublingual Tablet and you feel fully awake before driving." (PTX 50 at NOVZ0007894; Tr. 1.218:4–1.219:2 (Kryger)). At the outset, the Court notes that Defendants' argument that the driving study should be discredited simply because it was not conducted on Defendants' ANDA products is, again, dismissed. From a cumulative standpoint, Plaintiffs have met their burden of proving infringement of this element. To credit this conclusion, the Court points specifically to the following: 1) Defendants' ANDA products' bioequivalence data[11]; 2) the fact that each ANDA product contains the same amount of the active pharmaceutical ingredient (and undisputedly the only hypnotic agent) zolpidem tartrate; and 3) expert testimony that Defendants' ANDA products

[11] While true that bioequivalence alone, does not prove patent infringement, when viewed in light of the totality of the evidence, the Court concludes Defendants have infringed the '131 patent. *See Alza*, 388 F. Supp. 2d at 722.

are expected to produce no residual sedative effects at four hours after dosing and behave just as Intermezzo® did in the driving study.

According to the '131 Patent and confirmed by Dr. Kryger, a driving performance test is an accepted and reliable test in the art for evaluating residual sedative effects. (JTX 001 at 6:59–60; Tr. at 1.193:15–1.193:18 (Kryger)). Under the heading "Driving Study," Defendants' proposed labels each describe the study as:

> A randomized, double-blind, placebo-controlled, active-control, single-center, four period, crossover study in 40 healthy subjects was conducted to evaluate the effects of middle-of the-night administration of Zolpidem Tartrate Sublingual Tablets on next-morning driving performance. The four randomized treatments included Zolpidem Tartrate Sublingual Tablets 3.5 mg four hours before driving. . .

(Tr. 1.194:3–15 (Kryger); PTX 50 at NOVZ0007884). A double-blind study means that "the person and the experimenter do not know what treatment the person is on, whether they are on placebo or whether they are on a medication." (Tr. 1.194:19–1.195:6 (Kryger)). The results of the driving study showed that when driving began 4 hours after taking Intermezzo®, "statistically significant impairment was not found." (Tr. 1.197:24–1.198:18 (Kryger); PTX 50 at NOVZ0007884). Dr. Kryger explained that a POSA would understand the word "impairment" in this context to equate to residual sedative effects. (Tr. 1.198:12–18 (Kryger)). Thus, the labels' statement that there was no statistically significant impairment at 4 hours after dosing means that there were no residual sedative effects. (Id.).

Defendants, through their expert Dr. Winkelman, challenge the driving study as an acceptable measurement of sedation. First, Defendants claim that *Vermeeren* did not measure sedation at a time of about four hours after dosing because the protocol required that the test patients were awake and alert 45 minutes prior to starting the driving study, and occurred over the

course of 4 to 5 hours after administration. Second, Defendants argue that driving studies in the prior art literature that measured residual sedative effects did so based on the "statistically significantly different from placebo" standard rather than the symmetry analysis of subjects who change from their own SDLP (standard deviation of lateral position) as in *Vermeeren*. Many of these arguments overlap those made by Defendants relating to their indefiniteness argument of the same claim element. Because the Court finds a more detailed discussion is appropriate in the indefiniteness context, suffice it to say that with reference to Section II., C., 2., c., of this Opinion, the Court concludes that a driving performance test under these conditions is considered an accepted and reliable test in the art for evaluating residual sedative effects and the symmetry analysis used in *Vermeeren* is a persuasive measurement tool.

2. DSST

The Digit Symbol Substitution Test (DSST) is an accepted test of psychomotor performance in the art and one of the tests listed in column 6 of the '131 Patent. Plaintiffs point the Court to two articles by *Roth* to support a finding that the Defendants' ANDA products, which contain the same active ingredient at the same dosages used in those studies, would also test acceptably in a psychomotor performance test at 4 hours after dosing. A 2007 article by *Roth et al.*, published in the journal Human Psychopharmacology, found that both 3.5 mg and 1.75 mg zolpidem led to no residual sedative effects at 4 hours after dosing, as measured by the DSST. (Tr. 1.221:23–1.222:19 (Kryger); PTX 258 at PIZ00315144). In addition, a 2008 article by *Roth et al.* published in the journal Sleep described administering 3.5 mg and 1.75 mg doses of zolpidem to subjects and found that neither dose led to residual sedative effects at 4 hours after dosing. (Tr. 1.225:2–9 (Kryger); PTX 264 at JNTDEF0000559). Dr. Kryger opined that even when blood

plasma levels after subjects were given a 3.5mg dose or 1.75 mg dose of zolpidem are above 20 ng/ml [redacted] a composition can still pass DSST. Specifically, Dr. Kryger explained: "What we are looking at here is the DSST data. So even though the level was above 20, even though the level was above 20 at four hours, there was no abnormality with the DSST." (Tr. 1.227:18-23 (Kryger)). This evidence supports a finding that Defendants' ANDA products will test acceptably in the DSST psychomotor performance test and therefore infringe the '131 patent limitation "without residual sedative effects."

3. Defendants' Proposed Labelling

Defendants' proposed labels are virtually identical to that of Intermezzo®'s but for small changes such as replacing the word "Intermezzo" with another word describing the particular Defendant's product. Thus, the labeling Defendants submitted to the FDA for ANDA approval encourage infringement. The Parties' experts agree that there are no differences among the Defendants' labels that are relevant to the infringement analysis. (Tr. 1.175:11–1.176:2 (Kryger); Tr. 7.106:4–9, 8.175:16–21(Winkelman)). By providing instructions for use that when followed would lead to infringement, each Defendant would induce infringement under 35 U.S.C. § 271(b). *See, e.g., Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011) ("We have long held that the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent, and usually is also contributory infringement."); *AstraZeneca LP v. Apotex, Inc*., 633 F.3d 1042, 1060 (Fed. Cir. 2010) ("In the context of specific intent, . . . [t]he pertinent question is whether the proposed label instructs users to perform the patented method. If so, the proposed label may provide evidence of [an] affirmative intent to induce infringement.").

If Defendants truly believed their products would cause residual sedative effects, they could have pursued a non-infringing label. Defendants' proposed labels include statements indicating that it is safe for a patient to perform tasks requiring daytime awareness at 4 hours after dosing, which ultimately the Court finds to describe a lack of residual sedative effects. (Tr. 1.215:3–1.219:2 (Kryger)). Defendants' proposed labels also state: "Limitations of Use: Zolpidem Sublingual Tablet is not indicated for the treatment of middle-of-the-night insomnia when the patient has fewer than 4 hours of bedtime remaining before the planned time of waking." (PTX 50 at NOVZ0007870). Dr. Kryger explained that this statement implies that the patient can take the drug with 4 or more hours of time in bed remaining and wake up without residual side effects. (Tr. 1.215:11–1.216:7 (Kryger)). The Court too sees no alternative reading of the label. In further support of this point, Defendants' proposed labels also include a dosing time chart that tells patients when they would need to take the drug depending on when they have to get up. The dosing time chart tells patients that they must take the drug at least 4 hours before waking. (PTX 50 at NOVZ0007891–92; Tr. 1.216:25–1.218:3 (Kryger)).

As a matter of common sense, because Defendants' proposed labels instruct "[w]hen you wake up in the morning, be sure that at least 4 hours have passed since you have taken Zolpidem Tartrate Sublingual Tablet and you feel fully awake before driving," to argue that Defendants' ANDA products would produce residual sedative effects four hours after dosing would be juxtaposed to their labels' very warnings. This is evidence of infringement as well. To clarify, the Court is not suggesting that FDA regulations and patent laws can or cannot overlap. Production of a non-infringing product may be unsafe and compliance with FDA regulations may induce infringement. However, the two can be reconciled when appropriate. For instance, as indicated previously, having found that DRL's and Actavis' products do not contain "buffer,"

innovation beyond the '628 patent was promoted while safety was maintained. Such is not the case with the '131 patent and the limitation of no residual sedative effects. Should the Court find Defendants' products are likely to yield, by a preponderance of the evidence, residual sedative effects, the Court would also be finding that Defendants' proposed labels are inaccurate. The Federal Circuit also addressed this tension in concluding "[b]ecause drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1248 (Fed. Cir. 2000). Indeed, the aforementioned statements in Defendants' proposed labels indicate to patients that they will be free of residual sedative effects four hours after dosing therefore infringing the method delineated in the '131 patent.

4. Plasma Levels and Effects on Residual Sedative Effects

Defendants propose that [redacted] a POSA would conclude that residual sedative effects are likely to be present. However, while higher plasma concentrations can be indicative of residual sedative effects in some cases, Dr. Kryger explains that the problem with using the number 20 is that this number 20 "is really a safe harbor, and it is -- values below 20 would be considered a zero chance of having residual effect from that treatment, and values above 20, we don't know necessarily what they are." (Tr. 1.226:2-8 (Kryger)). In fact, Intermezzo® is an example of a product that when showing plasma levels of zolpidem above 20

nanograms per milliliter, is free from residual sedative effects at the appropriate time. (Tr. 1.226:24-1.227:2 (Kryger)). Additionally, to determine infringement, the Court's inquiry is directly related to the claim construction of the term. Here, the Court's claim construction is clear in stating that residual sedative effects can be evaluated by testing acceptably in one psychomotor test *or* demonstrating plasma levels of zolpidem below 20ng/ml. (Opinion, ECF No. 185 at 5-7) (emphasis added). Thus, this construction uses the word "or" to allow for more than one method of testing for residual sedative effects for the precise reasons articulated by Dr. Kryger, and a finding of infringement follows.

5. Remaining Uncontested Infringement Evidence

With regard to the '131 patent, Defendants only contested the "without residual sedative effects" limitation discussed above. However, the remaining elements of Claims 1 and 12, as well as asserted Claims 8, 10, 18 and 19 are also found to be infringed by Defendants. The Court first reiterates that all experts agree that there are no differences among Defendants' labels that are relevant to the infringement analysis. (Tr. 1.17511-1.76:2 (Kryger); 7.106:4-9, 8.175:16-21 (Winkelman)). With this is mind, Plaintiffs used Novel's label as representative of all Defendants' labels for purposes of the infringement inquiry.

Claims 10 and 19 require "delivery of zolpidem across the patient's oral mucosa." (JTX 001 at Claims 10 and 19). These claims are infringed for the same reasons articulated with regards to the '809 patent. (*See* Section I., B., 3., b., of this Opinion: "Specifically, four pieces of evidence regarding DRL's ANDA product—the dosing instructions (directing a patient to put the product under the tongue and allow it to "disintegrate completely"), higher early plasma concentrations than Ambien (avoid first pass effect), shorter lag time than Ambien, and higher Cmax than Ambien—prove that the zolpidem in DRL's ANDA product is delivered across the sublingual

mucosa. (*citing* Tr. 2.2.169:8–17 (Drover)). Defendants' proposed labels include an indication and usage for treating insomnia "when middle of the night awakening is followed by difficulty returning to sleep," therefore satisfying a method from treating MOTN insomnia in Claims 1 and 12. (*See e.g*. PTX 50 at NOVZ0007870). These labels also indicate usage for non-elderly patients (required by Claims 8 and 10) as well as elderly patients (required by Claims 18 and 19) "without prophylactically administering zolpidem," which is required by Claims 1 and 12. (Tr. 1.179:20-22, 1.80:10-17 (Kryger)). The quantities of zolpidem hemitatrate (required as a range in Claims 1 and 12, and 3.5 mg and 1.75 mg in Claims 8 and 18) are infringed for the same reasons expressed regarding the '809 patent and Defendants' labels. The only hypnotic agent (required by Claims 1 and 12) in Defendants' ANDA products is zolpidem tartrate. (Stip Facts ¶¶ 111, 116; Tr. 1.181:25-1.182:7 (Kryger)). Finally, Defendants' labels describe a patient desiring to resume sleep "for less than 5 hours," therefore satisfying all elements of Claims 1 and 12. Consequently, each of the asserted claims of the '131 patent are infringed by Defendants.

II. Patent Invalidity

A. Obviousness

"An obviousness analysis measures the difference between the claimed invention and the prior art to determine whether 'the subject matter as a whole would have been obvious at the time the invention was made' to a person having ordinary skill in the art." *Unigene Labs., Inc. v. Apotex, Inc*., 655 F.3d 1352, 1360 (Fed. Cir. 2011). Obviousness is a question of law based on underlying factual findings. *Honeywell Int'l, Inc. v. United States*, 609 F.3d 1292, 1297 (Fed. Cir. 2010). "The factual underpinnings, often referred to as the *Graham* factors, include: 1) the scope and content of the prior art; 2) the level of ordinary skill in the art; 3) the differences between the

claimed invention and the prior art; and 4) evidence of secondary factors, also known as objective indicia of nonobviousness." *Id.* at 1360.

"Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination. Rather, obviousness requires the additional showing that a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention." *Unigene*, 655 F.3d at 1360. Moreover, the party challenging validity must show that a person of ordinary skill in the art "would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and . . . would have had a reasonable expectation of success in doing so." *Procter & Gamble v. Teva Pharm.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quotation omitted). A claimed invention may, however, be obvious even when the prior art does not teach each claim limitation, so long as the record contains some reason that would cause one of skill in the art to modify the prior art to obtain the claimed invention. *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 728 (Fed. Cir. 2002). A finding of obviousness cannot, however, be based on "the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." *Crown Operations Int'l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir. 2002) (quoting *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998)).

"A person of ordinary skill at the time of the invention interprets the prior art using common sense and appropriate perspective." *Unigene*, 655 F.3d at 1361; *see generally KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-421 (2007) ("A person of ordinary skill is also a person of ordinary creativity, not an automaton."). In the same vein, although an analysis of the teaching, suggestion, or motivation to combine elements from different prior art references is helpful, this

Court's obviousness analysis requires an "expansive and flexible approach." *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1360 (Fed. Cir. 2012).

Finally, Defendants, as the patent challengers, must prove obviousness by clear and convincing evidence. *Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011). Clear and convincing evidence is a higher burden of proof than preponderance of the evidence. *See Colorado v. New Mexico*, 467 U.S. 310, 316 (1984). To be clear and convincing, evidence must "place[ ] in the factfinder 'an abiding conviction that the truth of [the] factual contentions are highly probable.' " *Procter & Gamble*, 566 F.3d at 994 (quotation omitted).

Defendants assert that the claimed invention is invalid for obviousness because the claims of the patents-in-suit would have been obvious to a POSA inasmuch as the scope and content of the prior art teaches all claimed elements. At trial, Defendants, "like all those who seek to prove claims obvious, was required to show that 'the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.'" *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737 (Fed. Cir. 2013) (citing 35 U.S.C. § 103).

Plaintiffs' main response to Defendants' obviousness challenge is that the claimed invention was not obvious because the prior art does not disclose: 1) efficacious low doses of zolpidem; 2) non-prophylactic dosing; and 3) transmucosal delivery of zolpidem. Plaintiffs also argue that a POSA would not have been motivated to combine the prior art because some references teach away from the claimed invention, nor would a POSA have had a reasonable expectation of success with low doses or transmucosal delivery of zolpidem. Finally, Plaintiffs ask the Court to consider the objective indicia of nonobviousness: licensing, industry

acquiescence, long-felt need and skepticism. While Plaintiffs as the party defending the patents-in-suit may offer evidence of secondary considerations of nonobviousness, these may not, by themselves, overcome a strong prima facie case of obviousness. *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010). For the reasons set forth below, the Court finds Defendants have proved a case of obviousness by clear and convincing evidence even after consideration of Plaintiffs' purported objective indicia of nonobviousness.

1. Person of Ordinary Skill in the Art

A person of ordinary skill in the art in the technology of the subject matter of the '131 patent is a person working in the field of sleep therapeutics and has: a least a Ph.D. in clinical psychology having at least one year of research experience in the field; or an MD having at least one year of clinical experience in the field. (Tr. 7.90:14-7.91:3 (Winkelman)). While Plaintiffs provided their own definition, both Parties' experts agree that none of their opinions concerning the '131 patent would change depending on which party's definition of a POSA is adopted.

On the other hand, a person of ordinary skill in the art to whom the '809 and '628 patent would be directed would have at least a bachelor's degree, and more likely a Master's or Ph.D. degree in pharmacy or a related science, and most likely several years of experience formulating active pharmaceutical ingredients, including some experience in transmucosal delivery. If this person of ordinary skill had a Bachelor's or Master's in pharmacy, or any other related subject, such a person would typically have more than five years of experience formulating active pharmaceutical ingredients. If they already had a Ph.D. in pharmacy, they would typically have fewer years of experience. If a person of ordinary skill in the art did not have actual experience with the developing transmucosal dosage forms, that person would at least have a deep knowledge

of the related scientific literature on the topic and be able to understand that scientific literature. (Tr. 6.31:1-24 (Michniak-Kohn)). While the Court employs Defendants' proposed definition, Plaintiffs' formulation expert agrees that his opinions on these patents would not alter depending upon which definition of a POSA was adopted. (Tr. 9.186:6-13 (Polli)).

2. Scope and Content of the Prior Art

In conducting the obviousness analysis, this Court views the claimed invention in light of the art that existed at the time the invention was made. *See* 35 U.S.C. § 103(a); *Uniroyal, Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050–51 (Fed. Cir. 1988). "Prior art has been defined as follows: '[t]he existing state of knowledge in a particular art at the time an invention is made. It includes the issued patents * * *, publications, and all other knowledge deemed to be common thereto such as trade skills, trade practices, and the like,' " available a year or more before the patent filing date." *Trio Process Corp. v. L. Goldstein's Sons, Inc.*, 461 F.2d 66, 69 n. 3 (3d Cir. 1972) (quoting A. Smith, PATENT LAW, CASES, COMMENTS AND MATERIALS 2 (1964)).

As previously stated, the asserted '131 and '809 patents are analyzed according to the prior art as of May 2005, while the '628 patent is compared to the prior art as of February 2004. The Court notes that none of the prior art described below is applicable to just one patent but not the others by virtue of its published date. The Court considers all the teachings in the prior art in the obviousness determination, "including that which might lead away from the claimed invention." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

It was well known by February 2004 that zolpidem was suitable for treating insomnia. Indeed, by that point in time, Ambien® (active ingredient being zolpidem tartrate) was the most popular sedative hypnotic for treating insomnia. The Ambien® label indicates it is used to "treat

different types of sleep problems" including "waking up often during the night." (JTX 41). Thus, before the priority dates of the patents-in-suit, a POSA would have been motivated to develop a treatment for MOTN insomnia that would be better than or as good as Ambien®. The Parties do not dispute that, given Ambien®'s success, a POSA aiming to treat MOTN insomnia specifically (or in the case of the '628 patent, insomnia generally) would have carefully considered the disclosures of Ambien® before or in conjunction with research of any additional prior art.

a. Ambien®

Ambien®, comprising the single hypnotic agent, zolpidem, was commercially released in 1992 and approved by the FDA "for the short-term treatment of insomnia." (JTX 041 at DRL0013526). Ambien® was the most successful drug for treating insomnia in 2004 where physicians prescribed Ambien® to 24 million patients. (Tr. 8.21:4-17 (Winkelman)). At the time of the invention, the recommended dose of Ambien® was 10 mg for non-elderly adults, and 5 mg for elderly adults. The Ambien® label indicates it is also effective to treat MOTN insomnia stating Ambien® "is used to treat different types of sleep problems, such as: trouble falling asleep; waking up too early in the morning; and *waking up often during the night*." (JTX 041 at DRL0013528) (emphasis added).

While it is undisputed that Ambien® was indicated for MOTN insomnia, Ambien®'s label instructed patients to take Ambien® at bedtime, therefore treating MOTN insomnia through prophylactic dosing. Specifically, Ambien®'s label stated: "Do not take Ambien unless you are able to get a full night's sleep before you must be active again." (JTX 029 at 3195). Further, the Ambien® label explains "Daytime drowsiness is best avoided by taking the lowest dose possible that will still help you sleep at night. Your doctor will work with you to find the dose of Ambien that is best for you." To Dr. Winkelman, this established the two main goals of a sleep aid:

effective to help the sleep problem but avoid residual sedative effects. (Tr. 7.164:3-24 (Winkelman) *quoting* JTX 041). Dr. Winkelman's assessment is both reasonable and credible to this Court.

As a general premise, Ambien® and the patents-in-suit, collectively, differ in three overarching ways. It is no surprise that these three differences are also the limitations Plaintiffs argue are either absent from the prior art or were taught away from by the prior art. First, Ambien® is an oral swallow tablet while the asserted claims of the patents-in-suit each provide delivery of zolpidem across the patient's oral mucosa. (*See* '131 Patent, JTX 001 at Claims 10 and 19; '809 Patent, JTX 002 at Claims 1, 11, and 12; '628 Patent, JTX 003 at Claim 1). Next, Ambien® is available in higher doses of 10 mg (for non-elderly) and 5 mg (for elderly) while the patents-in-suit disclose either the range of dose being 0.5mg to 5.0 mg of zolpidem, (*See* '131 Patent, JTX 001 at Claims 1 and 12; '809 Patent, JTX 002 at Claims 1 and 12; '628 Patent, JTX 003 at Claims 16 and 17), or 3.5 mg (for non-elderly) and 1.75 mg (for elderly). (*See* '131 Patent, JTX 001 at Claims 8 and 18; '809 Patent, JTX 002 at Claims 17 and 18). Finally, Ambien® is indicated for prophylactic administration while the '131 patent is a method to be used at the time of need, not prophylactically administering zolpidem. (*See* JTX001 at Claims 1 and 12). The Court now turns to a determination of whether it was obvious to treat MOTN insomnia by delivering zolpidem transmucosally, in low doses, and non-prophylactically. Based on the totality of the evidence presented, the Court is of the abiding conviction that in light of the prior art, these differences between Ambien® and the patents-in-suit were obvious to a POSA.

b. Prior Art Relevant to Transmucosal Delivery: *Tauber* and *Pinney*

Formulation for transmucosal delivery dates back to the 1902 treatment of angina. (Tr. 6.83:14-23 (Michniak-Kohn)). To formulate drugs for delivery across the oral mucosa, a POSA

would predict how much drug is available in its un-ionized form for a particular pH because "it is the un-ionized … that will actually cross membranes." (Tr. 6.84:12-15 (Michniak-Kohn)). In 1917, the Henderson-Hasselbach equation was established to aid in this function. Dr Michniak-Kohn described the Henderson-Hasselbach equation as "Chemistry 101," alerting the Court it was well within the knowledge of a POSA. (Tr. 6.84:22-25 (Michniak-Kohn)). This equation was used to provide a known pH range for un-ionized zolpidem based on a known p/k/a. (Tr. 6.161:2-10 (Michniak-Kohn)). Thus, the Court is convinced that once a POSA had the p/k/a, they could then conclude that most of the zolpidem will be unionized at pHs about above 7.8. (Id.).

In the same vein, the Court is also convinced that the efficiency of absorption of drugs in the oral cavity was explained by the prior art *Beckett* (1967), which disclosed raising the pH to promote absorption. (Tr. 6.85:8-20 (Michniak-Kohn)). Furthermore, the Parties do not dispute that sublingual tablets in general, were established well before 2003. (Tr. 6.73:22-24 (Michniak-Kohn)). However, the first disclosure of transmucosal delivery *in relation to the treatment of insomnia*, came in 1984. The 1984 *Tauber* study ("Plasma Levels of Lormetazepam After Sublingual and Oral Administration of 1 mg to Humans") measured plasma levels after oral administration of sublingual 1 mg lormetazepam ("sleeping wafer"). The results showed, on average, an earlier rise in the lormetazepam levels after sublingual administration as compared to oral, specifically, the sublingual dosage produced statistically higher levels between 7.5 and 25 minutes than the oral tablet. Therefore, *Tauber* ultimately concluded that "[i]t is anticipated that subligual administration of the new formulation will lead to 40-50% reduction of sleep latency." (Id. at 1587, 1591).

These findings aligned with the two requirements— according to *Tauber*—that from a pharmacokinetic point of view, a modern hypnotic should fulfill. These are the following: 1) "the

plasma levels of the active ingredient should increase immediately after administration to guarantee that the patient will fall asleep;" and 2) "after induction of sleep the plasma level of pharmacologically active substances should decay rapidly in order to reduce the possibility of hangover effects, drug accumulation and possible late interactions, e.g. with alcohol." (DTX 066 at 1587-1588). From a practical standpoint, *Tauber* described the clinical advantages of sublingual administration of hypnotics including: 1) convenient administration as "no glass of water is necessary;" 2) easy dissolution without leaving behind excess undissolved material; 3) rapid absorption through the oral mucosa, (avoiding the first-pass metabolism in the liver) resulting in "prompt onset." (Id. at 1596). These advantages to transmucosal delivery in the hypnotics context, continue to date. (*See also Zhang* (2002), JTX 038: "Oral transmucosal technology offers an alternative means for administering drugs. It allows more rapid absorption into the bloodstream than is possible with oral administration to the gastrointestinal tract. Oral transmucosal administration is noninvasive, nontechnical, and convenient for patients;" *see also* Tr. 9.70:11-21: (Moline), Agreeing with the conclusions of *Zhang.*)).

The prior art *Pinney* is a patent application dated November 29, 2001. The invention disclosed in *Pinney*, "Chewing Gums, Lozenges, Candies, Tablets, Liquids, and Sprays for Efficient Delivery of Medications and Dietary Supplements," is summarized as the following:

> A transmucosal delivery system according to the invention comprises a carrier suitable for oral administration. A buffer is dispersed within the carrier, and there is sufficient buffer to achieve a predetermined pH within the oral cavity of a user. An active ingredient is dispersed within the carrier, at least a portion of the active ingredient being unionized at the predetermined pH for transmucosal absorption within the oral cavity.

(DTX 062 at 4). *Pinney* confirms one advantage in *Tauber*, namely, that this system avoids the "first pass effect" through the liver of swallowed tablets which can lead to only a small fraction of

the amount of the active ingredient entering the bloodstream. (Id. at 1-2). Put differently, a higher bioavailability of active ingredients may be achieved by transmucosal delivery than by oral ingestion. (*See* Tr. 6.136:17-22 (Michniak-Kohn) Explaining that *Pinney* says you have to take into account the drug's bioavailability).

Pinney then goes on to describe ideal characteristics of active ingredients (acidic) and buffers (suggesting citric acid) but warns that "under pH conditions in the mouth (pH 6.0 to pH 7.0), many of the useful compounds would be highly ionized and would not be efficiently absorbed into the bloodstream by that transmucosal route." (Id. at 4, 6). *Pinney* denotes a pH of 7-10 in mouth conditions for "efficient absorption of most active ingredients." (Id. at 7). Specifically relevant, *Pinney* explains that "tablets" as in the patents-in-suit, are dosage delivery systems for medicants that are placed in the mouth or under the tongue for rapid dissolution of active ingredients and absorption through epithelial, where the "dissolution times" should be "preferably in the range of 5-15 minutes." (Id. at 8, 11). While *Pinney* lists zolpidem as a medicant suitable to transmucosal delivery, it does not specifically disclose how to formulate zolpidem nor is it targeted towards a method for treating insomnia. (Id. at 13).

c. Prior Art Relevant to Low Doses

At the time of the inventions, the lowest recommended dose of Ambien® and therefore zolpidem, was 10 mg for non-elderly adults, and 5 mg for elderly adults. Ambien® undoubtedly taught a POSA that the elderly should receive half the dose of zolpidem than a non-elderly patient. (*See also* Tr. 7.186:12-14: "[I]n the elderly, we need to lower the dose;" *citing Olubodun* (2003), JTX 026). However, these doses was for a full night's sleep (not half a night's sleep), taken at bedtime. At bedtime a person's drive to sleep is at its peak, as opposed to the middle of the night, after some sleep has occurred. This distinction results from the interaction of two biological

processes, the circadian drive and homeostatic sleep drive.[12] The *Borbély* model ("Figure 4"), published in *Borbély et al.*, "A two Process Model of Sleep Regulation," describes this interaction and its effect on a person's *overall* propensity to sleep. (DTX 211 at Fig. 4) (emphasis added). According to the *Borbély* model a person's drive for sleep—taking into account the homeostatic sleep drive and the circadian drive—is much greater at bedtime than in the middle of the night and therefore, it may be more difficult for a person to return to sleep.

As Ambien® was only prescribed for prophylactic dosing, one prior art reference suggested a way to combat MOTN insomnia even when one's sleep drive is lower. That is, Jacob Teitelbaum, M.D., published the book "From Fatigued To Fantastic," in 2001 which included a chapter where zolpidem was explained as a prescription medication to aid in "A Good Night's Sleep." (JTX 33 at 105, 115). *Teitelbaum* explained:

> I like Ambien [Zolpidem] because it is short-acting (that is, less likely to leave you hungover)… Because it is short-acting, it may not keep you asleep all the way through the night but will likely give you four to six hours of good, solid sleep as a foundation. The normal dosage is one-half to one 10 milligram tablet, taken at bedtime. If you wake up in the middle of the night you can take an *extra* one-half to one tablet (leave it by your bedside with a glass of water) and any sedation is usually worn off by the time you are ready to wake up in the morning. One-half tablet is usually enough for the middle of the night.

(JTX 33 at 115-116) (emphasis added). Thus, *Teitelbaum* suggests taking a total of 15 mg of zolpidem, 10 mg at bedtime and 5 mg in the middle of the night. However, *Teitelbaum*'s further guidance that "[o]ne-half tablet is usually enough for the middle of the night," certainly suggests that 5 mg is effective even when overall propensity to sleep is decreased. This is not surprising considering that the 1995 reference, *Roth et al.*, found 7.5 mg of zolpidem to be effective to treat

[12] Explained in "Background, V.," of this Opinion.

transient insomnia. (JTX 30).

Transient insomnia is "occasional episodes of acute sleep disturbance." (JTX 30 at 246). *Roth et al.*, "Zolpidem in the Treatment of Transient Insomnia: A Double-Blind, Randomized Comparison With Placebo," used a testing model known as the "first-night effect" to examine the effects of zolpidem (5, 7.5, 10, 15 and 20 mg) on transient insomnia in a large subject population. The "first-night effect" models transient insomnia in healthy subjects because subjects, on their first night in a sleep laboratory, will sleep less well. (*See* Tr. 10.96:19-10.97:9 (Czeisler)). Subjects were dosed with zolpidem or placebo at bedtime and then awakened 8 hours later to perform various tests. *Roth* only conducted statistical analysis of the 7.5 mg and 10 mg doses, but provided the resulting data related to sleep latency inclusive of the 5 mg dose in the table below:

TABLE 2 (JTX 30 AT 248) (OMITTED)

(JTX 30, "Table 2" at 248). *Roth* concluded that 7.5 mg and 10 mg doses of zolpidem were effective in treatment of transient insomnia. While *Roth* did not draw any conclusions related to the low 5 mg dose, in 1996, the *Walsh* article analyzed *Roth's* data stating: "Disregarding dose, zolpidem was highly effective in shortening latency to persist sleep and in reducing the number of

nighttime awakenings and time spent awake after sleep onset. These effects were highly significant in the groups that had received 7.5 of 10 mg zolpidem, but not in the 5 mg group (although numerical trends were evident at this dose." (PTX 282 at 130). Dr. Winkelman, however, concluded that the 5 mg dose in *Roth*, if a statistical analysis had been done, it would have been "statistically significant," and therefore, effective. (Tr. 7.221:18-7.222:10 (Winkelman)). Given the *Roth* (*see* "Table 2" above) data shows that 5 mg of zolpidem was shorter by 8 to 9 minutes than placebo in getting people to sleep, the Court agrees. (Tr. 7.220:18-20 (Winkelman)).

While intuitively a POSA may conclude from the *Borbély* model and *Roth* that higher doses may be needed in the middle of the night, this goal of efficacy must always be counterbalanced with the requirement of no residual effects in the morning. (*See* Tr. 7.145:11-19 (Winkelman) Part of being a physician is that with any drug "you always want the lowest effective dose," balancing a dose that is effective but also not giving a dose too high which results in side effects.). With this in mind, the relevant prior art as a whole,[13] including *Roth*, which Plaintiffs opine would lead a POSA away from low doses of zolpidem, was unconvincing to the Court. Thus, the Court finds that a POSA would undoubtedly attempt to find the lowest effective dose of zolpidem to avoid potential residual sedative effectives. Coincidently, the prior art reference *Merlotti*, set out to do just that.

Merlotti is titled: "The Dose Effects of Zolpidem on the Sleep of Healthy Normals." (DTX 063). In 1989, *Merlotti* performed a dose-ranging study for zolpidem in non-elderly, healthy

[13] A few redundant, unpersuasive, or disconnected references have been omitted from this Section for sake of brevity. The Court however, considered *all* the prior art admitted in evidence and explained by the experts at trial, prior to concluding.

(without insomnia) subjects. Before bed, subjects received zolpidem (2.5, 5.0, 7.5, 10.0 or 20.0 mg) or placebo. On the third night of each treatment, subjects always received placebo. *Merlotti* specifically sets out to address "what is the lowest dose of zolpidem that consistently produces hypnotic activity in normal volunteers?" (DTX-063 at 1). The study analyzed two measurements of sleep induction: 1) "wake before sleep," which is minutes of wake before persistent sleep; and 2) "latency to persistent sleep," which is minutes from the beginning of the recording to the start of the first 10 consecutive sleep minutes. (DTX-063 at 11).

As Dr. Winkelman explained, *Merlotti's* results showed the 5 mg dose of zolpidem was "statistically superior in getting people to sleep than placebo." (Tr. 7.170:18-21 (Winkelman)). *Merlotti* ultimately concluded that zolpidem is hypnotically active at doses lower than previously tested including the 5.0 mg dose. (*In contrast see Vogel* (1988): "[F]indings indicate that zolpidem was an efficacious hypnotic in the treatment of transient insomnia. Efficacy, defined as significant difference from placebo, usually occurred at doses of 7.5 mg and above. The drug improved both sleep latency and sleep maintenance. Its effect on sleep maintenance occurred only during the first 4 hours of bedtime." (JTX 036 at 67)).

Although the *Merlotti* study was done at bedtime, when sleep drive is at its highest, the prior art reference *Kim* tackled the issue of whether doses of hypnotics are hindered by less sleep drive. The *Kim* reference is titled: "Dose and Time Dependent Discrimination of Daytime Sleepiness Measured by Multiple Sleep Latency Test (MSLT), Psychomotor Performances Tests (PPT), and Stanford Sleepiness Scale (SSS) after a Single AM Administration of a Sedative Hypnotic Drug." (DTX 197). *Kim* explained that MSLT, PPT, and SSS index physiological, manifest, and introspective factors of sleepiness, but assessing these tests at peak drug effect after nighttime administration is confounded by the subjects' natural circadian drowsiness. Thus, in the

Kim study, MSLT, PPT, and SSS tests were performed to understand the dose and time dependent influence of zolpidem after AM administration in well-rested healthy volunteers. Zolpidem was administered in either a 5 mg or 10 mg doses (some received placebo) in the morning. The results showed that a significant decrease in sleep latency on the first four tests was found with zolpidem at both doses, so even the 5 mg dose of zolpidem was able to get subjects to sleep in statistically significantly shorter time than placebo. From these findings, the authors concluded: "In well-rested healthy volunteers, AM administration of zolpidem produced sedation as demonstrated by changes in physiological, manifest, and introspective measures of daytime sleepiness." (Id. at JNTDEF0006712).

Finally, because the patents-in-suit all differ from the aforementioned method of administration—*Teitelbaum, Roth* and *Merlotti* all observed zolpidem in its oral (swallow) form of administration—it is important to determine if a prior art reference would lead a POSA to understand an effective dose of systemic administration, specifically transmucosal administration. Defendants argue that this alternative route would be noted by a POSA to achieve the most rapid onset possible in the middle of the night and also avoiding residual sedative effects. Defendants assert that the change in administration can be reconciled by the prior art, *Patat*. (See Tr. 7.204:2-8 (Winkelman): Based on *Patat*, "[i]f you give systematic administration of zolpidem, you are going to get a more rapid appearance of indicators of sleep," as subligual is also one kind of systemic delivery). The *Patat* reference studied pharmacodynamics and pharmacokinetics of zolpidem after daytime administration both orally (swallow) and intravenous (IV). While *Patat* did not study transmucosal delivery, it did measure IV which is also systemic. Specifically, the *Patat* reference measured EEG (electroencephalogram) brain waves and results using the Stanford sleepiness scale (SSS). Appropriately, this 1993 prior art was titled "EEG profile of intravenous

zolpidem in healthy volunteers." (JTX 028).

As the method employed, subjects were given zolpidem in the morning (5 mg, 10 mg, or 20 mg) either by mouth to swallow (yielding 70% bioavailability) or intravenously (yielding 100% bioavailability) and required to stay awake throughout the study. *Patat* explained, "delta activity appeared rapidly 10 minutes after IV administration of zolpidem and between 20 and 45 minutes after oral administration of zolpidem." Delta waves are the slow waves that are present at the deepest stage of sleep (or delta activity). (Tr. 7.202:24-7.203:3 (Winkelman)). Thus, their slowing of the EEG showed significant sleepiness more quickly through IV administration. Additionally, the results of the SSS (describing how sleepy a person feels) show that at four hours after administration, the 5 mg dosage was no different from placebo indicating no expectation of residual sedative effects. In sum, the authors concluded that "EEG changes and scores of SSS were in good correlation with what has been observed with insomniac patients. Zolpidem has a rapid onset and a short duration of action, whatever the route and the dose." (Id. at JNTDEF0004144).

d. Prior Art Relevant to Non-Prophylactic Dosing

As previously stated, Ambien® was indicated for prophylactic administration. Prophylactical administration in this context refers to taking Ambien® every single night at bedtime "whether or not you are going to have insomnia that night." (Tr. 10.180:1-10 (Kryger)). Alternatively, non-prophylactic administration is pro re nata or "as-needed" dosing. (Tr. 10.180:11-19 (Kryger)). Prior to the filing of the patents-in-suit, the prevailing approach for treating insomnia was prophylactic administration. (*See e.g. Teitelbaum*, JTX 033 at 115-116: "normal dosage is one-half to one 10 milligram tablet, *taken at bedtime*." (emphasis added)). Further, even though Ambien® was indicated for treatment of MOTN insomnia, it only instructed

use at bedtime, not in the middle of the night. However, the disadvantages of prophylactic treatment and the need for flexibility in treating MOTN insomnia were well established in the prior art literature (*see below: Doghramji, Danjou, Hindmarch*) and clearly within the knowledge of a POSA. (*See e.g.* (Tr. 7.143:7-12 (Winkelman): "[F]or people who only wake up in the middle of the night sometimes, you're giving them medication when they don't need it, because how can you predict when you're going to wake up in the middle of the night."). But it remained clear that "as-needed" administration was in constant tension with lingering residual sedative effects.

***i. Danjou* Reference**

In 1999, *Danjou* purported to compare the duration of residual hypnotic and sedative effects of zaleplon with those of zolpidem (and placebo) following nocturnal administration at various times before morning awakening. The study used a 10 mg dose of zaleplon as well as a 10 mg dose of zolpidem, each administered orally (or swallowed). The subjects were then "gently" woken up—mimicking MOTN insomnia— at various times during the time and residual sedative effects were measured using the psychomotor performance and memory tests: digital symbol substitution test (DSST), critical flicker fusion (CFF) threshold, choice reaction time (CRT), memory test (word list), and Sternberg memory scanning. The results showed that no residual effects were demonstrated after zaleplon 10mg was administered as little as 2 hours before waking. Zolpidem 10 mg however, showed significant residual effects on DSST and memory after administration up to 5 hours before waking. Residual effects were also shown using CFF threshold and Sternberg memory scanning after administration up to 4 hours before waking. *Danjou* stated that the lack of residual sedative effects for zaleplon results are consistent with its pharmacokinetic profile featuring rapid absorption, distribution and clearance. Therefore, the

conclusion was that zaleplon at the 10 mg dose (recommended) dose, would "seem to provide physicians with a hypnotic free of residual effects at least in normal volunteers." (JTX 015 at JNTDEF0003922).

***ii. Hindmarch* Reference**

Similar to *Danjou*, *Hindmarch* was a study in 2001 where the objective was to assess residual effects of zaleplon and zolpidem after a middle of the night administration. Subjects received placebo, 10 mg or 20 mg of zolpidem, or 10 mg or 20 mg of zaleplon. The results showed that zaleplon 10 mg had no or minimal residual effects when administered in the middle of the night as little as one hour before waking. Zolpidem 10 mg produced significant detrimental residual effects in various tests when administered 3-5 hours before waking with the exception of the CFF test. The conclusion hypothesized that the lack of clinically significant residual effects with zaleplon may be explained by its unique pharmacokinetic profile of rapid elimination half-life, "providing some advantages over existing treatments[] for the management of insomnia and sleep disturbance… even when administered in the middle of the night." (PTX 256 at 166).

***iii. Doghramji* Reference**

The 2000 reference *Doghramji* is titled "The Need for Flexibility in Dosing Hypnotic Agents." (JTX 016). This prior art was not a clinical study but rather an article specifically targeting MOTN insomnia. *Doghramji* describes non-prophylactic dosing, stating "[t]he intermittent occurrence of most insomnia suggests that treatment is best accomplished by using hypnotics on an 'as needed' basis." (JTX 016 at JNTDEF0000168). This is because "[e]pidemiologic studies suggest that insomnia does occur on a regular basis in most people." (Id.

at JNTDEF0000168). Indeed, *Doghramji* touts the various advantages to "as needed dosing" to treat insomnia including: 1) optimal management while using the lowest amount of a drug; 2) providing a patient with a "sense of control" which prevents insomnia from being a "significant problem;" and 3) potentially reducing anticipatory anxiety prior to sleep. (Id. at JNTDEF0000170) (*See also Scharf* (2001): "hypnotic therapy administered prior to bedtime, as is currently recommended for most compounds, is not appropriate for all insomnia patients" (PTX 477 at 20))

Doghramji was limited to analyzing three hypnotics for flexible administration: triazolam, zolpidem, and zaleplon. Triazolam was dismissed from the onset because it is an agent with "drawbacks that are not ideal from treatment of insomnia." (Id. at JNTDEF0000169). Ultimately, it was determined that zaleplon is best suited for MOTN administration because of its half-life of one hour (while admitting that zolpidem has a rapid onset and short half-life). The article focuses on two trials conducted on zaleplon, (including *Danjou*), where a lack of residual sedative effects followed MOTN zaleplon administration. On the basis of these two tests, *Doghramji* concluded that "zaleplon appears to be suited for flexible use on an as-needed basis." (JTX 016 at JNTDEF0000171) (*See also Scharf*: "clinical trial data presented suggest zaleplon may represent an important breakthrough…Clinicians are now able to focus on a specific sleep disturbance by prescribing a medication that can be administered on intermittent nights only when symptoms occur—at bedtime or during the night—so long as 4 hours remain prior to a scheduled awakening." (PTX 477 at 23)).

3. Differences between the Prior Art and Claimed Invention

While it is clear that the prior art certainly fills in many of the prominent gaps between Ambien® and the patents-in-suit, some differences remain outstanding. First, while *Pinney* and *Tauber* teach transmucosal delivery of hypnotics, they do not teach how (or if) zolpidem can be

delivered this way. Next, while the Court is persuaded by clear and convincing evidence that *Merlotti* certainly concludes that lower doses of zolpidem such as 5 mg are effective, but the patents-in-suit specify even lower dose ranges and specific doses for non-elderly (3.5 mg) and elderly (1.75 mg). (*See e.g.* '131 Patent, JTX 001 at Claims 1 and 12; '809 Patent, JTX 002 at Claims 1 and 12; '628 Patent, JTX 003 at Claims 16 and 17). Finally, while *Doghramji*, *Danjou*, and *Hindmarch* teach that MOTN insomnia is best treated non-prophylactically, each of these references ultimately concludes that zaleplon—not zolpidem—is best suited for MOTN insomnia. In addition to pointing out these differences, Plaintiffs argue that there was no reasonable expectation of success in either transmucosal delivery of zolpidem, claiming this formulation is "unpredictable," or low effective doses, as a POSA, with knowledge of the *Borbély* model, would have assumed the dose must be increased when sleep drive is lower in the middle of the night. Plaintiffs also assert that claim-by-claim, a few additional elements— relevant to the '809 and '628 patent exclusively — are lacking in the prior art. The Court addresses each issue in turn.

a. Transmucosal Delivery of Zolpidem was Obvious to a POSA.

The Court finds that a POSA would have been motivated to achieve the most rapid action possible when formulating a drug to be taken in the middle of the night, as any delay in onset necessarily results in less sleep. When formulating a hypnotic, *Tauber* clearly explained that rapid onset is one of the main goals, stating, "the plasma levels of the active ingredient should increase immediately after administration to guarantee that the patient will fall asleep." (DTX 066 1587-1588). *Pinney* taught a POSA that transmucosal delivery would achieve the drug in the bloodstream within minutes of application (yielding high initial plasma levels), rather than approximately 30 minutes with conventional oral (swallow). (Tr. 6.139:16-20 (Michniak-Kohn)).

Indeed, Dr. Michniak-Kohn agrees that oral (swallow) administration results in the relief of symptoms being "substantially delayed," which would, in this Court's view, alert a POSA that transmucosal is faster. (Tr. 6.137:1-25 (Michniak-Kohn)). This evidence is clear and convincing to the Court.

At trial, Plaintiffs presented examples of different medicants—with the remarkable exclusion of zolpidem—which did not produce initially higher plasma concentrations in the sublingual dosage form. (*See e.g.* Tr. 9.110-9.112 (Drover) "[E]rgoloid mesylate[]… oral formulation generated a higher plasma concentration earlier than the sublingual formulation."). The Court finds this evidence unpersuasive as it fails to draw a parallel to zolpidem even though zolpidem tartrate's pharmacodynamics and pharmacokinetics were well understood, published and established by 2003. (Tr. 6.94:16-21 (Michniak-Kohn)). What is, however, most persuasive to the Court were the properties of zolpidem, as explained by Dr. Michniak-Kohn, that would indicate to a POSA that it can be delivered transmucosally. These include: 1)logP; 2) p/k/a; 3) solubility; and molecular weight. (Tr. 6.155:14-6.158:4 (Michniak-Kohn)).

The LogP, at 2.42, tells a POSA that zolpidem is lipophilic which means it passes more easily through membranes. (Tr. 6.156:9-23 (Michniak-Kohn)). P/k/a values of zolpidem were 6.9 and 6.16 which, when plugged into the Henderson-Hasselbach equation, calculate a value that predicts how much drug is available in its un-ionized form for a particular pH to cross membranes. (Tr. 6.157:1-23, 6.84:12-15 (Michniak-Kohn)). Zolpidem's molecular weight is 307.4 grams per mole which is a "suitable size for passing through mucosal membranes." (Tr. 6.158:4-12 (Michniak-Kohn)). Plaintiffs did not rebut this evidence. However, as it pertains to the final property, solubility, Plaintiffs suggest that a POSA would have not had a reasonable expectation of success in dissolving zolpidem tartrate in the mouth, which is required for delivery across the

oral mucosa. Defendants respond by pointing to the Material Safety and Database Sheet (MSDS) which shows that zolpidem solubility is "water solubility 23 mg per ml in water at 20 degrees centigrade." (DTX 302). Furthermore, Dr. Michniak-Kohn explains that there is at least 1 milliliter in the mouth and the mouth is warmer than 20 degrees centigrade so there "wouldn't be a problem to dissolve it." (Tr. 6.150:20-151:11 (Michniak-Kohn)). The Court finds these deductions rational and credible despite Plaintiffs' expert, Dr. Polli's vague criticism that Dr. Michniak-Kohn fails to take into account that zolpidem's solubility is going to be "pH dependent." (Tr. 9.1201:15-19 (Polli)).

In response to Plaintiffs' final objections to a finding that transmucosal delivery of zolpidem was reasonably expected by a POSA to be successful, the Court notes that the Federal Circuit has made clear that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). For this reason, Dr. Drover's claims that: 1) reformulating zolpidem for sublingual delivery is not obvious because the change in bioavailability is "not easy to predict;" (Tr. 9.137:3-12 (Drover)); and 2) the formulation is not obvious because transmucosal products are "not always successful," (Tr. 9.78:20-25 (Drover), are properly rejected by the Court in light of the aforementioned evidence which the Court finds clear and convincing. (Tr. 9.78:20-25 (Drover).[14] Consequently, the Court holds that a POSA would have a reasonable expectation of success in formulating zolpidem for transmucosal delivery.

[14] "Obviousness does not require absolute predictability of success," but rather, requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed.Cir.2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed.Cir.1988)).

b. A POSA would have Anticipated a Reasonable Expectation of Success with Low Doses of Zolpidem Based Upon Predictable Calculations.

As an initial premise, the Court finds that in light of *Danjou* and *Hindmarch*, a POSA seeking to treat MOTN insomnia non-prophylactically with zolpidem, would have been motivated to lower the 10 mg dose to eliminate the residual sedative effects. (*See e.g.* (Tr. 7.198:1-3 (Winkelman) *Hindmarch* shows that if you want to give a dose in the middle of the night, "10 [mg] is too much…you should lower the dose." (Tr. 7.198:1-3 (Winkelman)). Further, as *Merlotti's* 5 mg dose of zolpidem (or a half dose of Ambien®) was shown to be effective, a POSA would begin their hunt for the lowest effective dose with 5 mg. (*See also* Tr. 7.146:14-15: Referring to Ambien® doses, Dr. Winkelman explained "full night, 10 milligrams. Half night, 5 milligrams. I mean, it is very simple math."). Plaintiffs however, are correct in their contention that there is no *single* prior art reference before the Court teaching a POSA that 3.5 mg and 1.75 mg doses are effective. In this context, the Court must therefore determine if these lower doses were obvious to a POSA. The Court finds that they were.

i. Lowering the Dose from 5.0mg to 3.5mg and 2.5mg to 1.75mg

In conjunction with the prior art references *Merlotti* and *Patat*, Defendants cite to a POSA's knowledge of dose optimization of zolpidem tartrate based on zolpidem's known physical and chemical properties, including linear pharmacokinetics and available dose information. (*See e.g.* Tr. at 8.23:5-8.25:10, 8.26:4-7 8.16:12-8.17:1, 8.25:15-8.26:10). In sum, a transmucosal dose of 3.5 mg of zolpidem is appropriately compared to a 5 mg oral dose of zolpidem because the bioavailability of zolpidem is 70%, and 70% of 5 mg is equal to 3.5 mg. (Tr. 6.112:15-6.113:4 (Michniak-Kohn)). Dr. Michniak-Kohn explained that from *Patat*, you would use the 70%

bioavailability figure of zolpidem and multiply it by the 5 mg dose (published in *Merlotti*) and it would yield 3.5 mg of zolpidem for non-elderly and then 70% multiplied by half of the 5 mg dose (2.5 mg) would yield 1.75 mg for elderly. (Tr. 6.129:7-21, 6.130:16-21 (Michniak-Kohn)). Thereafter, she concluded, and this Court agrees, that a POSA would have a "reasonable expectation that th[ese] [calculations] would succeed" in translating the known low dose from oral to transmucosal while maintaining efficacy. (Tr. 6.132:3-8 (Michniak-Kohn)). Indeed, even the inventor of the patents-in-suit referred to this as "*a simple calculation*." (Tr. 5.73:20-5.74:2 (Singh) (emphasis added)).[15]

Plaintiffs, nevertheless, argue that these calculations are misplaced as the bioavailability for sublingual zolpidem is actually around 75%, not 100% as calculated by Dr. Michniak-Kohn and Dr. Winkelman. The Court's conclusion is unfettered by this argument. The proper inquiry before the Court is not whether the calculations are correct, but rather whether they would have been obvious to apply and therefore yield the lowest doses. Dr. Winkelman explained that sublingual doses put the drug on the blood vessels and it gets absorbed right into the bloodstream so "[i]t is not the same as intravenous but it is quite close." (Tr. 7.204:9-12, 7.208:14-17 (Winkelman)). Knowing that intravenous would yield 100% bioavailability, it is credible and reasonable to find that it would be obvious to a POSA to use 100% to yield a predicted dose for sublingual form. Therefore, the Court is convinced that the lower doses of zolpidem are obvious.

[15] The Court notes that in this context, Dr. Singh's statement is taken into consideration to establish that the calculations were well within the knowledge of a POSA. The Court does not refer to Dr. Singh's statement without the proper anti-hindsight perspective.

ii. Reasonable Expectation of Success

Plaintiffs argue that a POSA would assume low doses of zolpidem would not be successful in effectively putting one back to sleep in the middle of the night. Plaintiffs point the Court to *Teitelbaum* and the *Borbély* model for this premise claiming a POSA would expect that a subject would need *more*, not less zolpidem in the middle of the night because their sleep drive is less. Plaintiffs' expert, Dr. Czeisler concludes that a POSA "would have expected to use certainly at least the same dose [of 10 mg or 5 mg zolpidem], if not a higher dose [of zolpidem], in the middle of the night because of the decrease in homeostatic sleep drive and the muting of the circadian system." (Tr. 10.83:10-23 (Czeisler)). *Teitelbaum* seems to suggest something similar in stating: "the normal dosage is one-half to one 10 milligram tablet, taken at bedtime. If you wake up in the middle of the night you can take an extra one-half to one tablet (leave it by your bedside with a glass of water) and any sedation is usually worn off by the time you are ready to wake up in the morning." (PTX 033). However, *Teitelbaum* concludes this suggestion with, "one-half tablet is usually enough for the middle of the night." (Id.). This runs contrary to Dr. Czeisler's suggestion that one would need higher or equal to a 10 mg dose in the MOTN and is plainly stated in the prior art.

Finally, the *Kim* reference tested zolpidem in the morning, when one's sleep drive would be at its very least and concluded that 5 mg zolpidem was able to get patients to sleep statistically significantly shorter than placebo, therefore demonstrating its efficacy regardless of sleep drive. The Court therefore is persuaded by Dr. Winkelman's "common sense" suggestion that if a subject "wanted to sleep for half a night, four hours, [they] would take half of the dose that [they] would for a full night." (Tr. 7.146:10-13 (Winkelman)). In sum, there is, before this Court, clear and convincing evidence that there was a reasonable expectation of success in treating MOTN

insomnia by taking less amounts of zolpidem in the middle of the night.

c. *Doghramji, Danjou,* and *Hindmarch* Do Not Teach Away from Zolpidem at the Doses Claimed.

Where, as here, the claim limitations are found in a combination of prior art references, this Court, as the factfinder, must determine "[w]hat the prior art teaches, whether it teaches away from the claimed invention, and whether it motivates a combination of teachings from different references." *In re Fulton,* 391 F.3d 1195, 1199–1200 (Fed.Cir.2004). While the Court is cognizant that as a "useful general rule," references that teach away cannot serve to create a prima facie case of obviousness, a POSA seeking to treat MOTN insomnia by a better means than Ambien® would inevitably use non-prophylactic dosing. *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130 (Fed.Cir.1994). This is because MOTN insomnia as a "condition wherein a subject, after falling asleep, awakens and has difficulty returning to sleep," is so entangled with treatment "as-needed" as it is impossible to know, *until the middle of the night*, whether the insomnia will occur. (ECF No. 92 at 2). This principle, in and of itself, is convincing to the Court that non-prophylactic administration was obvious. Nevertheless, the Court also concludes that the relevant prior art references do not teach away from zolpidem.

The Court agrees with Defendants that *Doghramji*, *Danjou*, and *Hindmarch* all promote the benefits of taking a hypnotic agent on an "as needed" basis. The studies in *Danjou* and *Hindmarch* each dosed a subject in the MOTN, representative of non-prophylactic administration at bedtime. Specifically, *Danjou* is directed to "nocturnal administration" and *Hindmarch* to "middle of the night administration." (JTX 015 at 367, PTX 256 at 159). *Hindmarch* also references "[p]atients having sleep maintenance problems or difficulties falling asleep, especially after being awakened during the night." (PTX 256 at 160). Lastly, *Doghramji* explains that

hypnotic agents are typically given "prophylactically prior to going to bed," but now the "availability of a new hypnotic agent with a short half-life" (although, referencing zaleplon) suggests a patient may be able to take the agent during the night. (JTX 016 at JNTDEF0000171-172). However, as Plaintiffs correctly point out, the ultimate conclusion of each of these references was that zaleplon was better suited for MOTN administration due to the lingering residual sedative effects produced with zolpidem.

A reference "teaches away" when it "suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Medichem, S.A. v. Rolabo, S.L.,* 437 F.3d 1157, 1165 (Fed.Cir.2006) (quoting *In re Gurley,* 27 F.3d 551, 553 (Fed.Cir.1994)). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley,* 27 F.3d 551, 553 (Fed.Cir.1994). Whether a prior art reference teaches away from the claimed invention is a question of fact. *Para–Ordnance Mfg., Inc. v. SGS Imps. Int'l, Inc.,* 73 F.3d 1085, 1088 (Fed.Cir.1995).

The Court however, concludes that a POSA would not be deterred from these findings. The key basis for this conclusion is that *Danjou, Doghramji, and Hindmarch,* each tested the higher 10 mg dose of zolpidem for MOTN administration and their findings and subsequent recommendations were based solely on residual sedative effects. Even Plaintiffs' expert admits that a POSA would know that a lower dose of zolpidem would decrease the time that hypnotic effects would occur. (Tr. 10.54:19-24 (Czeisler)). Certainly, a POSA would not disregard the touted benefits of non-prophylactic dosing to achieve their ultimate goal simply because the final conclusion of a reference chooses zaleplon at a dose *more than double* that of the claimed

invention. (*See also* Tr. 6.108:2-9 (Michniak-Kohn) *Doghramji* leads a formulator to "decrease the dose" as they knew they wanted the drug to wear off in four hours.). Additionally, both Parties' expert agree there are specific disadvantages to zaleplon, and Plaintiffs' experts have failed to offer persuasive evidence that a POSA would consider zaleplon over zolpidem given Ambien®'s success and known efficacy. (*See* Tr. at 1.161:21-1.162:9 (Kryger), Tr. 7.156:18-157:6 (Winkelman)). Viewed against the backdrop of the totality of collective teachings of the prior art and the common knowledge of a POSA that reducing the dose would reduce residual sedative effects, *Danjou, Doghramji, and Hindmarch* do not teach away from zolpidem in a manner that would deter a person of ordinary from combining these references with the low doses articulated in *Merlotti.*

d. Buffer Claims of the '628 and '809 Patents

The Court refers to the "Buffer Claims," in its obviousness analysis with reference to: 1) Claim 1 of the '628 patent's limitation "wherein the buffer raises the pH of saliva to a pH of about 7.8 or greater;" 2) Claim 9 of the '628 patent identifying "the buffer comprises a carbonate buffer and bicarbonate buffer;" and 3) Claim 22 of the '809 patent requiring the composition to contain a "binary buffer system." Plaintiffs assert that these Claims are not obvious for interrelated reasons. Plaintiffs oppose a finding that Claim 1 of the '628 patent is obvious because of the requirement that the pH be elevated to above 7.8, which they maintain, was not established by clear and convincing evidence. With reference to Claim 9, Plaintiffs argue that while *Pinney* identifies 13 individual buffering agents, it fails to disclose or render obvious zolpidem combined with a "carbonate buffer and bicarbonate buffer," as required by the Claim.

Similarly, pursuant to Claim 22 of the '809 patent, the composition must contain a "binary

buffer system that raises the pH of said subject's saliva to a pH greater than about 8.5, irrespective of the starting pH of saliva." The Court construed a "binary buffer system," in Claim 22 of the '809 patent to mean "a system used to maintain and/or achieve an approximate pH range comprising at least one proton-donating component and at least one proton accepting component." (Opinion, ECF No. 185 at 26). Plaintiffs purport that is was not obvious to "raise[] the pH of said subject's saliva to a pH greater than about 8.5." The Court does not agree with Plaintiffs for the following reasons.

Pinney expressly teaches a specific pH range in the mouth—between 7 and 10—for efficient oral administration through the oral mucosa. (Tr. 6.139:21-6.140:15 (Michniak-Kohn)). Thus, the pH values of 7.8 and 8.5 are well within *Pinney's* claimed ranges. The Federal Circuit has made clear that if the relevant comparison between disputed claim limitations and the prior art pertains to a range of overlapping values, "we and our predecessor court have consistently held that even a slight overlap in range establishes a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1329 (Fed.Cir.2003). This Court follows suit.

Additionally, evidence before the Court established that the carbonate/bicarbonate buffer in Claim 9 of the '628 patent (or binary buffer for purpose of the '809 patent) was a well-known buffer as of 2003 and how to make a buffer to raise the oral cavity to a desired pH when administering a transmucosal drug was well within the knowledge of a POSA would know. (Tr. 6.144:6-21 (Michniak-Kohn)). *Beckett* for example, teaches a binary buffer used to raise the pH (while *Beckett* uses phosphate buffer, bicarbonates are very common in use). (Tr. 6.145:14-24 (Michniak-Kohn)). *Pinney* also teaches a formulator to use a pH-raising agent in the oral mucosa for transmucosal delivery. (Tr. 6.133:1-11 (Michniak-Kohn)). Even the inventor, Dr. Singh, cooreberates that Dr. Michniak-Kohn's understanding was within the knowledge of a POSA. He

explains that changing the pH by way of a buffer for transmucosal delivery is "basic chemistry." (Tr. 5.64:10-18 (Singh)). Moreover, the Court declines to ignore the *Pinney* disclosure of this specific buffer among just 13 options. While the Federal Circuit has predicated a finding of nonobviousness on a sheer number of variable combinations, it did so in the face of a prior art disclosure of a "potentially infinite genus." *In re Baird*, 16 F.3d 380, 382 (Fed.Cir.1994) (quoting *In re Jones*, 958 F.2d 347, 350 (Fed.Cir.1992)). The case at bar does not remotely approach an infinite genus, as it is quantifiable in just 13. The Court therefore finds the Buffer Claims were obvious in view of the above.

e. '809 Patent: Outstanding Claim Elements of Claims 1, 12

The composition claimed in the '809 patent must contain, among other things, an effective amount of zolpidem "sufficient to produce a plasma concentration between about 25 ng/mL and about 50 ng/mL within 20 minutes of administration when evaluated in an appropriate patient population." (JTX 002 at Claims 1 and 12). Plaintiffs argue that Dr. Michniak-Kohn's assertion that the 20-minute plasma concentrations are "inherent" in the doses (3.5 mg and 1.75 mg) is both incorrect and unsupported by data. Plaintiffs scold Dr. Michniak-Kohn for failing to consider that pharmacokinetic parameters will depend on the specifics of the formulation, not just the dose of the drug. (Tr. 9.140:13-22 (Drover)). Remarkably, however, Dr. Drover subsequently admits that he is not a formulation expert. (Tr. 9.140:20 (Drover)).

Regardless, a closer look at Dr. Michniak-Kohn's testimony reveals that based upon the linear pharmacokinetics, presented in a demonstrative graph in fact used by Dr. Drover, she opined that a POSA could easily predict offset blood concentrations for sublingual doses because when you "half the dose… that means half the plasma concentration at the same point." (Tr. 6.111:15-

19 (Michniak-Kohn)). This is contrary to Plaintiffs' blanket assertion that the only evidence before the Court was inherency in the dose. (*See also* Tr. 6.112:1-7: Predictions of offset blood concentrations can be done with zolpidem because a POSA the pharmacokinetics of zolpidem known by 2003 were "linear enough." (Michniak-Kohn)). Dr. Michniak-Kohn further points to plasma concentrations for Ambien®, the *Merlotti* reference and *Patat* reference, to explain that a POSA would take into account the dose *as well as the bioavailability data*. (*See e.g.* Tr. 7:46:1-17 (Michniak-Kohn)). Specifically, Dr. Michniak-Kohn explains how a POSA would understand that *Patat* reported the blood concentration of 20 nanograms for a male as the onset and offset threshold for sedation of zolpidem (referring to the concentration at which zolpidem begins to start sedating or stop sedating a patient). (Tr. 6.87:16-20 (Michniak-Kohn). Indeed, the plain text of *Patat* states:

> [R]eturn to baseline also occurred at concentrations ranging from 20 (5 mg PO or IV) to 75 ng.ml (20 mg PO). As the EEG effects are very rapid, whatever the dose or the route of administration, it can be suggested that the threshold concentration of zolpidem was already attained.

(JTX 028 at JNTDEF0004150). Indeed, 20 nanograms, viewed in light of *Patat* as the lowest concentration cited for onset/offset sedation—with a total range of 20-75 ng/ml—the claimed range of between "about 25ng/ml and about 50ng/ml" naturally flows and is disclosed. *See e.g.*, *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (concluding that a claimed invention was rendered obvious by a prior art reference whose disclosed range ("about 1–5%" carbon monoxide) abutted the claimed range ("more than 5% to about 25%" carbon monoxide)). This Court therefore finds Dr. Michniak-Kohn's reading of Patat—and determination that it renders this element of Claim 1 obvious—to be both credible and convincing.

It is important to also bolster this finding with a case where the Federal Circuit has even

previously upheld such an "inherent property" on similar facts. In *Santarus, Inc. v. Par Pharm., Inc.,* 694 F.3d 1344 (Fed. Cir. 2012) the court identified that "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations." *Id.* at 1351; *see also In re Kao 639* F.3d 1057, 1070 (Fed. Cir. 2011) ("To hold otherwise would allow any formulation—no matter how obvious—to become patentable merely by testing and claiming an inherent property."). Distinctly though, neither party disputed that the blood serum concentrations claimed in *Santarus* were expected in light of the dosages disclosed in the prior art. *Id.* However, here, the Court finds that in light of the dosages delineated in the '809 patent and *Patat*, the concentrations in the '809 patent are disclosed, if not inherent, and therefore obvious.

4. Motivation to Combine

As stated, MOTN insomnia was previously being treated the same way as other types of insomnia, prophylactically. The uniqueness inherent in MOTN insomnia however, is that a person will not know at bedtime—when prophylactic doing occurs—if they are going to experience it. Such prophylactic dosing therefore leads to overmedication and drug dependence. (*See e.g.* Tr. 1.52:9-24 (Kryger)). Thus, the problem in the context of the patents-in-suit, was to develop a method and composition for treating MOTN insomnia exclusively while avoiding the downfalls of prophylactic administration.

The Court finds that a POSA would have been motivated to combine Ambien® with the prior art references to solve this problem. The record at trial clearly established that a skilled person seeking to formulate a drug to treat MOTN insomnia had 4 well-known goals: 1) administer the drug on an as-needed basis (upon MOTN wakening); 2) employ an active ingredient that was known to deliver rapid onset of action to get one back to sleep as quickly as possible; 3) use the

lowest effective dose; and 4) avoid residual sedative effects upon awakening. (*See e.g.* Tr. at 8.11:6-22; 8.12:4-8.13:7 (Winkelman)). In order to achieve the aforementioned goals, a POSA, at the time of the invention—armed with the knowledge of the prior art—would use low-dose zolpidem (*Merlotti* and Ambien®) administered in the middle of the night (*See e.g. Danjou* and *Doghramji*) in a formulation that is delivered across the oral mucosa (*Pinney* and *Tauber*). (Tr. at 8.25:13-8.26:12 (Winkelman)). This methodology suffices to establish a motivation to combine as such motivation does not have to be explicitly stated in the prior art, and can be supported by testimony of an expert witness regarding knowledge of a POSA at the time of invention. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1294 (Fed. Cir. 2006).

However, Plaintiffs' further claim that a POSA would not be motivated to combine low doses of zolpidem with a transmucosal delivery system because zolpidem was already known to have rapid action. Contrary to this assertion, the record indicates a number of benefits to sublingual administration, particularly in the hypnotics context. To name a few, *Tauber* found a 40-50% decrease in sleep latency and *Pinney* found transmucosal delivery would achieve the drug in the bloodstream within minutes of application, rather than approximately 30 minutes with oral. (*See also* Tr. 7.142:1 (Winkelman) After middle of the night awakening, the "clock is ticking" to fall back asleep.). Viewed as a whole, a POSA would have been motivated to make a version of Ambien® that could be used solely for MOTN insomnia. Organically, the combination of the pertinent prior art references did just that.

5. Prima Facie Case of Obviousness

As articulated above, the Court finds that Defendants have presented clear and convincing evidence that the asserted claims of each of the patents-in-suit are obvious and these patents as a

whole are obvious. Giving the elderly half the dose of the non-elderly was taught by Ambien® and substantiated by the knowledge of a POSA. The claims relating to transmucosal delivery are obvious in light of *Pinney*, *Tauber*, the *Henderson-Hasselbach* equation, and the known (and widely published) properties of zolpidem. Thus, the relevant elements of Claims 10 and 19 of the '131 patent, Claims 1, 11, and 12 of the '809 patent, and Claim 1 of the '628 patent are obvious. The claim ranges and specific low doses of zolpidem are obvious in view of *Merlotti, Patat* and a POSA's knowledge of dose optimization of zolpidem tartrate, (including linear pharmacokinetics and Dr. Michniak-Kohn's and Dr. Winkelman's calculations). Subsequently, these elements of Claims 1, 8 and 18 of the '131 patent, Claims 1, 18 and 17 of the '809 patent, and Claims 16 and 17 of the '628 patent are obvious.

The Court is cognizant that a claimed invention may be obvious even when the prior art does not teach each claim limitation, so long as the record contains some reason that would cause one of skill in the art to modify the prior art to obtain the claimed invention. *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 728 (Fed. Cir. 2002). The record has convinced the Court of just that, grounded in the clear goals of targeting the specific insomnia occurring only in the middle of the night. Even so, the remaining elements and claims specific to each patent are also obvious. Non-prophylactic dosing in Claims 1 and 12 of the '131 patent are obvious based upon *Doghramji, Danjou* and *Hindmarch*, as well as the nature of MOTN insomnia. The Buffer Claims, in light of *Pinney* and *Beckett*, render Claim 22 of the '809 patent and Claims 1 and 9 of the '628 patent, invalid as obvious. Finally, the remaining element of Claim 1 of the '809 patent, namely, plasma concentration of 25 ng/ml to 50 ng/ml within 20 minutes, is invalid in light of *Patat*.

6. Secondary Considerations

With Defendants having met their burden to establish a *prima facie* case of obviousness, the Court will go on to consider the fourth *Graham* factor: facts regarding objective indicia of nonobviousness. It is well-settled that "all evidence relevant to obviousness or nonobviousness be considered, and be considered collectively." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1078. As they can give "light to the circumstances surrounding the origin of the subject matter sought to be patented," *Graham*, 383 U.S. at 17–18, 86 S.Ct. 684, objective considerations serve as a check against hindsight bias and " 'may often be the most probative and cogent evidence in the record.' " *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1075–76, 1079 (quoting *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed.Cir.1983)). Indeed, these considerations can have the force of " 'establish[ing] that an invention appearing to have been obvious in light of the prior art was not.' " *Id.* at 1075–76 (quoting *Stratoflex*, 713 F.2d at 1538–39). The Court will now consider each of the objective considerations raised by the Parties.

a. Licensing, Industry Aquiescence, Commercial Success

Plaintiffs rely on the license deal between Purdue and Transcept as well as other licensing "offers" and "interest" to support a finding of nonobviousness. (PFOF ¶¶ 650-655). Primarily, the Court notes that in accordance with *In re GPAC Inc.*, 57 F.3d 1573 (Fed.Cir.1995), licenses "may constitute evidence of nonobviousness; however, only little weight can be attributed to such evidence if the patentee does not demonstrate a nexus between the merits of the invention and the licenses of record." *Id.* at 1580 (internal quotations and citations omitted). Plaintiffs have failed to convince the Court of such nexus. Moreover, whatever little significance the licenses may have is clearly outweighed by the strong evidence of obviousness found in the prior art. *See Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1131 (Fed.Cir.2000).

When further viewed in conjunction with Intermezzo®'s lack of industry praise and lack of commercial success, the Court is not inclined to give one licensing deal much weight. Indeed, "'the mere existence of ... licenses is insufficient to overcome the conclusion of obviousness' when there is a strong prima facie case of obviousness." *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1324 (Fed.Cir.2004) (citing *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1358 (Fed.Cir.2000). Actual sales for Intermezzo® are under $10 million while the market projections suggested sales of Intermezzo® in 2015 of $495 million. (Tr. 2 .113:2-3 (Oclassen), 9.15:10-23 (Kraft)). This striking disparity is significant as the Federal Circuit has noted that commercial success " 'is usually shown by significant sales in a relevant market.' " *J.T. Eaton & Co. v. Atlantic Paste & Glue Co.*, 106 F.3d 1563, 1571 (Fed.Cir.1997). Needless to say, Intermezzo® is far from reaching a significant sales mark. Plaintiffs have also failed to point to credible evidence of industry praise, reassuring the Court that this factor, as a whole, weighs in favor of obviousness.

b. Long-Felt Need and Failure of Others

"Long-felt need is closely related to the failure of others. Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1082 -1083 (Fed. Cir. 2012). Failure of others "to find a solution to the problem which the patent[ ] in question purport[s] to solve" is evidence of nonobviousness. *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed.Cir.1991) (internal quotation marks and citation omitted). The problem the patents-in-suit sought to solve is a targeted treatment for MOTN insomnia only, where treatment can be taken "as needed." At the outset, the Court notes that Plaintiffs have provided no evidence of failure of

others to solve this problem and therefore rely solely on their theory there was a long-felt and unmet need for treating MOTN insomnia.

Prior to the filing of the patents-in-suit, Ambien® was used to treat MOTN insomnia prophylactically. The Court admittedly observed a number of downsides to prophylactic treatment at trial, including overmedication. (Tr. 1.52:9-24 (Kryger)). Furthermore, the prior art references such as *Doghramji* (and *Scharf*), clearly articulated a need for flexibility to treat MOTN insomnia on an "as-needed" basis. (*See e.g.* JTX 016). However, while Plaintiffs point the Court to these references, *Doghramji* was published in 2000 and *Scharf* in 2001. This is just four years prior to the filing of the patents-in-suit. Thus, the Court concludes that the intervening time between the prior art's teaching of the "as needed" treatment and the eventual preparation of a successful composition, is hardly "long-felt." (*See Ecolochem, Inc. v. S. Cal. Edison Co.*, The length of the intervening time between the publication dates of the prior art and the claimed invention can also qualify as an objective indicator of nonobviousness. 227 F.3d 1361, 1376–77 (Fed.Cir.2000)).

c. Skepticism

"General skepticism of those in the art ... is also 'relevant and persuasive' evidence of nonobviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH,* 139 F.3d 877, 885 (Fed.Cir.1998) (internal quotations and citation omitted). This is so because "[p]roceeding contrary to the accepted wisdom is ... strong evidence of unobviousness." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 668 (Fed.Cir.2000) (internal quotation marks and citation omitted). In support of their skepticism argument, Plaintiffs direct the Court to: 1) the prior art which indicated zolpidem for treatment of MOTN insomnia would likely lead to residual sedative effects; (*See e.g. Danjou* JTX 015); and 2) the maker of Ambien®, Sanofi's, licensing discussions with Trancept expressing "very substantial skepticism" according to Mr. Oclassen, Trancept's former CEO. (Tr.

2.69:23-2.70:1 (Oclassen)). The Court finds neither of these compelling.

As previously articulated, the prior art references indicating that zolpidem would produce residual sedative effects when administered in the middle of the night were only directed at the high doses of 10 mg (for non-elderly) and 5 mg (for elderly). No reference convinced the Court that zolpidem at lower doses would result in residual sedative effects, or that a POSA would believe so. Further, Mr. Oclassen's statement of "substantial skepticism" is rebutted by the record. (*See e.g.* Tr. at 2.219:1-14 (Garegnani) Explaining that the technology associated with making Intermezzo® "seemed very straightforward and kind of [] easy...;" Tr. 2.75:17-20 (Oclassen). For instance, it was known prior to 2004 that avoiding the first-pass effect by going from an oral swallow administration to transmucosal administration would increase bioavailability and allow for lower doses. (*See Pinney*). The Court is therefore unconvinced that the literature or testimony predating the filing of the patents-in-suit should be credited for a finding of skepticism.

7. Conclusion of Obviousness

For the reasons set forth above, the Court concludes that Defendants have made a *prima facie* showing that the asserted claims of the patents-in-suit would have been obvious in view of the prior art, the clear motivation to combine the references, and a reasonable expectation of success in doing so. The Court also finds that the Plaintiffs' evidence of secondary considerations is inadequate to raise any doubt as to the obviousness of these claims. The objective indicia presented really lent more evidence towards obviousness and thus most certainly did not carry sufficient weight to override a determination of obviousness based on primary considerations. Each patent-in-suit, when viewed as a whole, it therefore invalid.

B. Anticipation

Defendants argue that Claim 9 of the '628 patent should be invalidated as anticipated by the prior art reference *Pinney*. Claim 9 of the '628 patent recites as follows: "The method of claim 1, wherein the buffer comprises a carbonate buffer and a bicarbonate buffer." (JTX 003, Claim 9). Claim 9 is also dependent on independent Claim 1 which states the following:

> Claim 1: A method for treating insomnia, comprising the steps of: administering a solid pharmaceutical composition comprising zolpidem or a pharmaceutically acceptable salt thereof to a subject prone to insomnia, the pharmaceutical composition further comprising a buffer, wherein the buffer raises the pH of saliva to a pH of about 7.8 or greater, wherein zolpidem is absorbed across a permeable membrane of the subject's oral mucosa, and wherein at least 75% of the solid pharmaceutical composition dissolves within 10 minutes or less within an oral cavity following administration.

(JTX 003, Claim 1). *Pinney* was published in 2001 and is undisputedly prior art to the patents-in-suit. *Pinney* is titled "Chewing gums, lozenges, candies, tablets, liquids, and sprays for efficient delivery of medications and dietary supplements." (DTX 062).

1. Legal Standard

Pursuant to 35 U.S.C. §§ 102, a claimed invention is "anticipated," and is therefore not novel if it "was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant" or "was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. §§ 102(a)-(b). "A patent is invalid for anticipation if a single prior art reference

discloses each and every limitation of the claimed invention," and "a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed.Cir.2003) (internal citation omitted). In order to demonstrate anticipation, the proponent must show "that the four corners of a single, prior art document describe every element of the claimed invention." *Xerox Corp. v. 3Com Corp.,*, 458 F.3d 1310 1322 (Fed. Cir. 2006)(quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000)). Anticipation is a question of fact, *Sanofi–Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed.Cir.2008) (internal citation omitted), that must be established at trial by clear and convincing evidence. *Purdue Pharma L.P. v. Boehringer Ingelheim GmbH*, 237 F.3d 1359, 1365 (Fed. Cir. 2001).

2. *Pinney* Fails to Anticipate Each and Every Limitation of Independent Claim 1.

Defendants argue that *Pinney* enables the method of treatment claimed in the '628 patent. This is significant because a claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003). However, Defendants argument that the *Pinney* reference is anticipatory ignores a few key differences between the '628 patent and *Pinney*. Therefore, the Court concludes that Plaintiffs have demonstrated that the asserted claims survive the validity challenge posed by the *Pinney* reference.

While Plaintiffs concede that some of the elements of the '628 patent are in fact disclosed and therefore anticipated by *Pinney*, Plaintiffs persuasively argue that two elements are missing. First, Plaintiffs claim *Pinney* fails to indicate that that transmucosal absorption of zolpidem is even possible, let alone disclosing how to accomplish this function. Next, Plaintiffs contend that *Pinney*

fails to disclose any relation to "insomnia" and therefore does not disclose "methods of treating insomnia" in a subject "prone to insomnia," but rather, one would need to supplement *Pinney* with another reference, such as the Ambien® label, to arrive at the claimed invention. Because anticipation requires a more stringent finding than obviousness—by limiting the inquiry to one prior art reference—the Court agrees with Plaintiffs on these points in the limited context of anticipation.[16]

Plaintiffs argue that because the pharmacokinetics of transmucosal formulations are unpredictable to a POSA viewing *Pinney*, and therefore it fails anticipate Claim 1 of the '628 patent as it does not teach how zolpidem can be formulated for transmucosal absorption. This Court agrees. It cannot be disputed that zolpidem fails to appear as the forefront of *Pinney*. Zolpidem is merely mentioned in a long list of potential active ingredients for a composition. (DTX 062 at 17). Thus, while true that *Pinney* mentions zolpidem, it does not present any findings or guidance on how or if zolpidem can be absorbed transmucosally.

Dr. Drover explained that bioavailability is key to proper development of this type of transmucosal formulation, although he claims an increase in bioavailability will not always be achieved when switching from an oral swallow tablet to a transmucosal formulation. (Tr. 9.102:5–9.104:6, 9.106:16–9.110:3, 9.122:13–9.123:17 (Drover)). Dr. Michniak-Kohn agrees in part, stating *Pinney* tells a formulator to take into account the drug's bioavailability for transmucosal delivery. (Tr. 6.136:17-22 (Michniak-Kohn)). However, the only known bioavailability of

[16] *See e.g. In re Fracalossi*, 681 F.2d 792, 794 (CCPA 1982); Although a claimed invention can be obvious but not anticipated, it "*cannot have been anticipated and not have been obvious.*" (emphasis added).

zolpidem comes from another reference, *Patat*, which is impermissible for a finding of anticipation.

Similarly, Plaintiffs' formulation expert Dr. Polli explained that a POSA would not understand *Pinney* to teach that each of the 160 listed active ingredients can be delivered transmucosally, as acetaminophen, a medicant listed in *Pinney*, is therapeutically effective at a dose of hundreds of milligrams, far too large a dose to be considered a candidate for oral transmucosal delivery. (DTX 062 at JNTDEF0004166; Tr. 9.193:22–9.194:2 (Polli)). The Court is constrained to agree based on the legal standard for anticipation. This is because Defendants' expert, Dr. Michniak-Kohn admits the need for additional information outside of *Pinney* to conclude zolpidem can be formulated for transmucosal delivery as *Pinney* provides "no data about zolpidem." (Tr. 9.198:19 (Polli); *See* Tr. 6.155:14-6.158:4 (Michniak-Kohn: Properties of zolpidem that would indicate to a POSA that it can be delivered transmucosally include: 1) logP; 2) p/k/a; 3) solubility; and molecular weight.).

In the same vein, *Pinney* cautions that "many active ingredients display chemical properties that prevent transmucosal absorption," yet, as Dr. Michniak-Kohn agreed, *Pinney* does not identify which of the actives display such chemical properties. (DTX 062 at JNTDEF0004155). The only formulation specifically disclosed in *Pinney* is a chewing gum for delivery of nicotine. (DTX 62 at JNTDEF0004167–69; Polli Tr. 9.195:18–20.) The Federal Circuit explained in *In re Omeprazole Patent Litigation*, 483 F.3d 1364 (Fed.Cir.2007) that "anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must necessarily include the unstated limitation, [or the reference] cannot inherently anticipate the claims." 483 F.3d 1364, 1378 (Fed.Cir.2007). This Court therefore agrees with Plaintiffs that transmucosal absorption of

zolpidem is not inherent in *Pinney* for Defendants have failed to convince the Court that this limitation would *necessarily* be recognized.

Pinney is also devoid of explicit instructions to treat insomnia. Indeed, during her analysis of obviousness, Dr. Michniak-Kohn admits that when designing the dosage for a formulation of a sedative hypnotic, the general method she would use would begin with reading up on the indication. (Tr. 6.81:6-22 (Michniak-Kohn)). Thus, a formulator would first need to be directed to insomnia literature before *Pinney,* as *Pinney* fails to give a POSA the indication of the '628 patent. With an established need to consult sources other than *Pinney* to find "each and every element as set forth in the claim[s]," no finding of anticipation shall issue. *Verdegaal Bros., Inc. v. Union Oil Co.,* 814 F.2d 628, 631 (Fed.Cir.1987).

In sum, *Pinney* does not anticipate the '628 patent because the prior art method did not dictate that zolpidem could be absorbed transmucosally nor the indications of insomnia. Here, Plaintiffs are claiming a method that consists of a new way of using a previously known process of delivery. While *Pinney* discloses the transmucosal delivery process, it fails to clearly indicate this process to treat insomnia or for delivery of *zolpidem*. The '628 patent required a POSA to exercise a combining of other prior art references to formulate zolpidem to absorption transmucosally and thus, for anticipation, "will not be denied the merit of patentability." *Quoting Ansonia Brass & Copper Co. v. Elec. Supply Co.*, 144 U.S. 11, 18, 12 S.Ct. 601, 36 L.Ed. 327 (1892).

C. Indefiniteness

Defendants claim "without residual sedative effects" is an indefinite claim term, therefore rendering the '131 patent invalid. As previously indicated, each of the claims of the '131 patent

asserted by Plaintiffs contain the limitation "without residual sedative effects," construed by this Court to mean "with no or minimal subjective feelings of sedation, as evaluated by: (a) testing acceptably in at least one test exploring psychomotor performance, attention, information processing, and memory used by those of skill in the art (hereinafter "Part A"); and/or (b) demonstrating plasma levels of zolpidem, at an appropriate time point, below about 20 ng/ml," (hereinafter "Part B"). (Opinion, ECF No. 185 at 5-7). The '131 patent lists the following psychomotor performance, attention, information processing, and memory tests (Part A tests):

> a Sleep Latency Test (SLT), a Visual Analog Test (VAT), a Digit Symbol Substitution Test (DSST), a Symbol Copying Test (SCT), a Critical Flicker Fusion threshold test (CFF), a Simple Reaction time test (visual or auditory; SRT), a Choice Reaction Time test (CRT), a Word Learning Test (WLT), a Critical Tracking Test (CTT), a Divided Attention Test (DAT), a digit or letter cancellation test, sleep staging through polysomnographic (PSG) measurements, Continuous Performance Task test (CPT), Multiple Sleep Latency Test (MSLT), a Rapid Visual Information Processing test (RVIP), a mental calculation test, a body sway test, a driving performance test, and others.

(JTX 3 at 6:45-60). According to Defendants, at the zolpidem doses claimed in the '131 patent, the presence or absence of infringement will depend on which of the various psychomotor performance, attention, information processing, and memory tests are administered. Defendants therefore conclude that because these tests will prove "outcome-determinative" of the infringement inquiry, the claim term is invalid as indefinite. This Court is not convinced of same.

1. Legal Standard

35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." The U.S. Supreme Court has held that courts should hold a claim to be

indefinite and therefore, invalid, "if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Nautilus, Inc. v. Biosig Instruments*, No. 13-369, 2014 U.S. LEXIS 3818, at *6 (June 2, 2014).

Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. *Halliburton Energy Servs., Inc. v. M-I LLC*, 514 F.3d 1244, 1249 (Fed. Cir. 2008). Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. *Athletic Alternatives, Inc. v. Prince Mfg., Inc.*, 73 F.3d 1573, 1581 (Fed.Cir.1996) ("[T]he primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.' ") (quoting *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, (1938)). In other words,

> [a] patent holder should know what he owns, and the public should know what he does not. For this reason, the patent laws require inventors to describe their work in "full, clear, concise, and exact terms," 35 U.S.C. § 112, as part of the delicate balance the law attempts to maintain between inventors, who rely on the promise of the law to bring the invention forth, and the public, which should be encouraged to pursue innovations, creations, and new ideas beyond the inventor's exclusive rights.

Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 731, 122 S.Ct. 1831, 152 L.Ed.2d 944 (2002).

The focus of indefiniteness rests on the meaning that claim terms would have to one of ordinary skill in the art. *Energizer Holdings, Inc. v. Int'l Trade Comm'n*, 435 F.3d 1366, 1370 (Fed.Cir.2006). However, "[e]ven if a claim term's definition can be reduced to words, it is still indefinite if a person of ordinary skill in the art cannot translate the definition into meaningfully

precise claim scope." *Halliburton Energy Servs., Inc. v. M–I LLC*, 514 F.3d 1244, 1251 (Fed.Cir.2008). Claims that are "insolubly ambiguous" are indefinite and therefore invalid. *Id.* at 1250 (quoting *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347 (Fed.Cir.2005)). An issued patent is presumed valid and, therefore, invalidity must be proven by clear and convincing evidence. 35 U.S.C. § 282; *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365 (Fed.Cir.2004).

2. "Without Residual Sedative Effects" is Not Indefinite.

Defendants present the Court with four somewhat interwoven arguments for indefiniteness. Each argument pertains to the potential for divergent results as to whether or not there are residual sedative effects at 4 hours after dosing. This conclusion, Defendants claim, is "outcome determinative" of the infringement inquiry under *Honeywell v. International Trade Commission*, 341 F.3d 1332 (Fed.Cir.2003) (hereinafter "*Honeywell*") and the claim term must be deemed indefinite. Specifically, Defendants argue: 1) that the Part A and Part B results may conflict; 2) there are "limitless" methods of testing for residual sedative effects under Part A; 3) the *Vermeeren* driving study exemplifies a test where results conflicted depending on the statistical method employed; and 4) the *Danjou* reference evidences divergent results between two Part A tests for the same dose of zolpidem. After Defendants' arguments and their factual underpinnings are analyzed by the Court, a review of the holding in *Honeywell* and its distinguishing facts is appropriate. Ultimately, the Court finds the evidence Defendants cite to for these propositions does not meet the clear and convincing standard.

a. Part A vs. Part B

Defendants first argue that the same formulation can test acceptably in a psychomotor performance test (claim construction Part A) and therefore infringe this limitation, while, at the same time, produce a blood plasma concentration (showing the amount of drug in the blood) higher than 20 ng/ml (claim construction Part B), therefore evidencing non-infringement. However, as previously articulated by the Court in its summary judgment Opinion on the same topic, this contradiction simply leads to a finding of infringement of the claim as the Court intentionally construed the claim with use of the conjunctive term "and/*or*," to allow for such. (emphasis added).

In line with this construction, the evidence produced at trial convinced the Court that 20 ng/ml is not a bright line test for residual sedative effects, but rather a safe harbor. Figures 1, 3, and 4 of the '131 patent itself depict the results of a DSST test and zolpidem blood levels following administration of a 3.5 mg dose of zolpidem and show that at four hours the blood level concentration of zolpidem was greater than 20 ng/mL but the results of the DSST test had returned to normal. Dr. Kryger explained that a return to baseline levels of impairment is possible despite an elevated blood level of zolpidem because the amount of impairment will depend on the level of zolpidem in the brain, *not in the blood*, due to the "blood-brain barrier." (emphasis added) (Tr. 1.227:3–1.229:22 (Kryger)). Indeed, Figure 4 of the patent shows that the change in DSST score had returned to baseline at four hours even though zolpidem blood levels remained above 20 ng/mL, therefore demonstrating that impairment will disappear even though zolpidem may remain in the blood. With this in mind, Defendants' indefiniteness argument must be confined to only Part A; psychomotor performance, attention, information processing, and memory tests.

b. Part A Does Not Delineate Limitless Methods

The '131 patent lists many psychomotor performance, attention, information processing, and memory tests and concludes by stating "and others." Defendants take issue with this phrase, claiming it establishes that there are "limitless" tests for infringement and thus, the term must be rendered invalid as indefinite. (Defs.' Proposed Findings of Fact ("DFOF") ¶ 478). Defendants cite to Dr. Winkelman's testimony specifying other "Part A" tests such as the Stanford Sleepiness Scale (as used in the *Patat* reference) and the Go/No Go Test. (Tr. at 7.97:1-17 (Winkelman); JTX 028 at 139). However, having a wide number of tests is not the standard to render a claim indefinite as "[b]readth is not indefiniteness." *In re Gardner*, 57 427 F.2d 786, 788 (1970). In any event, Defendants have not offered evidence that either of these tests, the Stanford Sleepiness Scale nor the Go/No Go Test, would produce divergent results from any of the other aforementioned tests. For this reason, Defendants' argument fails.

However, the crux of Defendants' position for indefiniteness rests on the notion that because "testing acceptably in at least one" of the Part A tests is sufficient to demonstrate that the patient will awaken at four hours after dosing "without residual sedative effects," a zolpidem composition may still infringe this limitation, despite failing one or more of the Part A tests, so long as the "possibility" exists of passing "at least one test" among the limitless set of Part A tests for residual sedative effects. (DFOF ¶ 479). In support, Defendants point the Court to the *Vermeeren* driving study and the *Danjou* reference at trial, claiming that in each of these, the tests exploring psychomotor performance, attention, information processing, and memory used by those of skill in the art, produced divergent results. While the Court finds the evidence at trial failed to demonstrate this proposition by clear and convincing evidence, the Court takes each of the references in turn.

c. *Vermeeren* Driving Study

As previously explained, a study called *Vermeeren* was conducted on Intermezzo® which, after MOTN administration, analyzed the driving performance of subjects to gage residual sedative effects that occurred the morning after. (PTX 252). It is undisputed that this type of driving study is one of the Part A tests used to measure residual sedative effects as set forth in the '131 patent itself. At trial, Plaintiffs presented the *Vermeeren* study to show that 4 hours after dosing, subjects were free from residual sedative effects. On the other hand, Defendants contend that the driving study in fact produced divergent results, evidencing the indefiniteness of the claim term "without residual sedative effects." More specifically, Defendants, through their expert Dr. Winkelman, purported that *Vermeeren* demonstrates both the existence and the absence of residual sedative effects, depending on the statistical measurement employed.

The two standards of measurement at issue are as follows: 1) determining whether the standard deviation of lateral position ("SDLP") (i.e. weaving) was statistically significantly different from placebo (i.e. there were residual sedative effects); and 2) driving impairment based on a McNemar symmetry analysis. Both Parties agree that the McNemar symmetry analysis conducted in the driving study demonstrates a lack of residual sedative effects. This means that the claim limitation "without residual sedative effects" is met, or, alternatively, would be infringed. However, Defendants argue that the SDLP data of the same study *does* show residual sedative effects, and therefore there are divergent results. Upon thorough review of *Vermeeren* as well as the testimony of Plaintiffs' relevant expert Dr. Kryger and Defendants' relevant expert Dr. Winkelman, the Court cannot agree with Defendants.

Vermeeren states the following:

> Results showed that when ZST (Intermezzo) was taken 4 h before driving, there was no statistically significant difference in the

> proportions of impaired and improved drivers. The mean SDLP at that time was significantly higher than PBO, but the overall increase was small (0.83 cm), and the 95% CI was well below the 2.5 cm threshold for impairment (95% CI, 0.1-1.15cm) … Overall, the data support that driving at least 4 h after taking ZST 3.5 mg, consistent with labeling instructions, does not negatively affect driving performance.

(PTX 252 at 494). To rebut the clear finding of *Vermeeren* that there were no residual sedative effects 4 hours after dosing, Defendants presented the testimony of Dr. Winkleman who explained the McNemar symmetry analysis is not the accepted standard in the industry and the SDLP measurement raw data showed statistically significant difference between Intermezzo and placebo at 4 hours. (*See e.g.* Tr. 7.115:18-22 (Winkelman)). Dr. Winkelman therefore concluded that *Vermeeren* showed Intermezzo® did not test acceptably in SDLP. (Tr. 7.109:1-7 (Winkelman)). However, the conclusion of *Vermeeren* found the opposite. *Vermeeren* used the mean SDLP data by applying a threshold of impairment of 2.5 cm (described as the standard in the art) and found no impairment. According to Dr. Kryger, *Vermeeren*'s conclusions are correct because the raw SDLP data is not determinative of clinically meaningful *impairment* in the patient population. The Court finds no reason not to analogize "impairment" with "residual sedative effects" in the driving study. All in all, Defendants' proposed discrepancy is not an inherent measurability problem, but rather a dispute between experts as to whether the measurements of *Vermeeren* were correctly performed, which certainly does not amount to indefiniteness.

d. *Danjou* Reference

At trial, Defendants used the *Danjou* reference in an attempt to illustrate the point that depending on the chosen Part A test, the same dosage amount will result in two divergent results. To Defendants, these contrary results, if true, indicated the presence of residual sedative effects

(non-infringing) while also indicating an absence of residual sedative effects (infringing). Specifically, in *Danjou*, 10 mg oral zolpidem "tested acceptably" in the DSST test four hours after administration, but the same dosage amount did not "test acceptably" in the Critical Flicker Fusion and the Choice Reaction Tests. (JTX 015 at Figs. 1, 2, 3). At the summary judgment stage, this Court previously dismissed the use of *Danjou* as demonstrating outcome-determinative results because *Danjou* did not test residual sedative effects for the low doses of zolpidem at issue (3.5 mg and 1.75 mg), but rather 10 mg dose. Because Defendants have failed to link the data in *Danjou* to the low doses of the '131 patent, the Court, again, rejects Defendants' argument as unpersuasive. The claim limitation "without residual sedative effects" of the '131 patent is not invalid for indefiniteness as Defendants have failed to meet their burden of proving invalidity, in this regard, by clear and convincing evidence.

e. *Honeywell v. International Trade Commission*

The Court distinguishes *Honeywell* for purposes of completeness. *Honeywell* involved a patent disclosing "a process for production of a particular multifilament polyester product called polyethylene terephthalate ("PET") yarn" used as a reinforcement for automobile tires. 341 F.3d at 1334. All claims in the patent at issue in that case "require[d] that the yarn produced by the claimed process fall within a specified . . . [melting point elevation] at some point during the process." *Id.* at 1335. The dispute in the case "focused on the method of measuring one claimed feature—the melting point elevation ("MPE")." *Id.* Although there were four methods for preparing PET yarn that were well known to persons of ordinary skill in the art, "neither the claims, the written description [of the patent at issue], nor the prosecution history reference[d] any of the four sample preparation methods that can be used to measure the MPE." *Id.* at 1339. In *Honeywell*,

the court noted that depending upon which method was used, "the calculated MPE for a given sample can vary greatly." *Id.* at 1336. With this in mind, the court held that the claims containing the disputed term "melting point elevation" were "insolubly ambiguous, and hence indefinite" because "the claims, the written description, and the prosecution history fail[ed] to give . . . any guidance as to what one of ordinary skill in the art would interpret the claim to require." *Id.* at 1340.

Contrary to the facts of this case, in *Honeywell* there was evidence that the method of preparation and testing was critical to the measurement, and that only one of the four methods produced a measurement within the claimed range; whereby the court concluded that the claims were "insolubly ambiguous, and hence indefinite." *Id.* at 1340. Here, the only credible and pertinent evidence before the Court showed consistent results. The Court will not appease Defendants and find indefiniteness based on a hypothetical possibility for inconsistent results. Such is far from the clear and convincing standard. As the Federal Circuit has previously held, "there is the potential for inconsistent results even within the same method of measurement, but that surely does not render a claim indefinite." *Takeda Pharm. Co. v. Zydus Pharm. USA, Inc*., 743 F.3d 1359, 1367 (Fed. Cir. 2014). Finally, in *Honeywell* it was shown that persons in the field of polymer chemistry understood that polymer melting point determinations vary significantly with the method used, rendering the claims "insolubly ambiguous." In contrast, it was not credibly disputed that persons in the field of the '131 patent would fail to understand how to measure residual sedative effects by the Part A tests. *Honeywell* is therefore distinguishable.

CONCLUSION

After a careful consideration of all the evidence presented at trial and for the reasons stated above, the Court concludes that Defendants have met their burden of proving the '131, '809, and '628 patents are invalid as obvious by clear and convincing evidence. The Court further finds that Defendants have failed to prove that the claim element "without residual sedative effects" of the '131 patent is invalid as indefinite. Defendants have also failed to prove the '628 patent is invalid as anticipated. The Court, however, finds that Plaintiffs have proved by a preponderance of the evidence that the asserted claims of the '131 patent are infringed by all Defendants, but also finds that Plaintiffs have failed to meet their burden of proving infringement of the '628 patent as to Defendants DRL and Actavis only. Novel is found to infringe the '628 patent. As to the '809 patent, Plaintiffs have met their burden of proving infringement as to Defendant, DRL and Defendant, Novel.

This Court's Opinion will be filed under temporary seal. The Opinion will be unsealed on Monday, April 20, 2015 unless an appropriate motion to seal same (pursuant to Local Civil Rule 5.3(c)) is filed by either of the Parties by April 17, 2015.

An appropriate Order accompanies this Opinion. Counsel are hereby directed to submit a proposed form of judgment consistent with this Opinion.

s/ Jose L. Linares
Jose L. Linares
United States District Judge

Date: March 27, 2015